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PTO/SB/50 (1-00)

Approved for use through 09/30/00, OMB 0651-0033

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## REISSUE PATENT APPLICATION TRANSMITTAL WITHOUT FEE OR OATH

## Address to:

Assistant Commissioner for Patents  
Box Patent Application  
Washington, DC 20231  
Box: REISSUE

Attorney Docket No.	IWA-126-USAP
First Named Inventor	Chikao NISHINO
Original Patent Number	5,814,634
Original Patent Issue Date (Month/Day/Year)	09/29/1998
Express Mail Label No.	

APPLICATION FOR REISSUE OF:  
(Check applicable box)

Utility Patent

Design Patent

Plant Patent

## APPLICATION ELEMENTS

1.  Fee Transmittal Form (PTO/SB/56)  
(Submit an original, and a duplicate for fee processing)
2.  Applicant claims small entity status. See 37 CFR 1.9 and 1.27.
3.  Specification and Claims (amended, if appropriate)
4.  Drawing(s) (proposed amendments, if appropriate)
5.  Reissue Oath/Declaration (original or copy)  
(37 C.F.R. § 1.175) (PTO/SB/51 or 52) (submitted  
Original U.S. Patent without signature)
6.  Offer to Surrender Original Patent (37 C.F.R. § 1.178)  
(PTO/SB/53 or PTO/SB/54)  
or  
 Ribboned Original Patent Grant  
 Statement of Loss (PTO/SB/55)
7. Original U.S. Patent currently assigned?  
 Yes  No  
(If Yes, check applicable box(es))  
 Written Consent of all Assignees (PTO/SB/53 or 54)  
 37 C.F.R. § 3.73(b) Statement  Power of  
Attorney

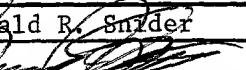
## ACCOMPANYING APPLICATION PARTS

8.  Foreign Priority Claim (35 U.S.C. 119)  
(if applicable)
9.  Information Disclosure Statement (IDS)/PTO-1449  Copies of IDS  
Citations
10.  English Translation of Reissue Oath/Declaration  
(if applicable)
11.  Preliminary Amendment
12.  Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
13.  Other: .....  
.....  
.....  
.....

## 14. CORRESPONDENCE ADDRESS

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Zip Code	20036-7613		
Fax	202-347-7870		

NAME (Print/Type)	Ronald R. Snider	Registration No. (Attorney/Agent)	24,962
Signature			Date 9/28/2000

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PTO/SB/56 (12-97)

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REISSUE APPLICATION FEE TRANSMITTAL FORM				Docket Number (Optional) IWA-126-USAP				
Claims as Filed - Part 1								
Claims in Patent	For	Number Filed in Reissue Application	(3) Number Extra	Small Entity		Other than a Small Entity		
				Rate	Fee	Rate	Fee	
(A) 26	Total Claims (37 CFR 1.16(j))	(B) 26	**** 6 = x \$ =			x \$ 18.00	108.00	
(C) 2	Independent Claims (37 CFR 1.16(l))	(D) 2	* = x \$ =			x \$ =		
				Basic Fee (37 CFR 1.16(h)) \$		\$ 690.00		
				Total Filing Fee \$		OR \$ 798.00		
Claims as Amended - Part 2								
	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity		Other than a Small Entity	
					Rate	Fee	Rate	Fee
Total Claims (37 CFR 1.16(j))	***	MINUS **	* =	x \$ =		x \$ =		
Independent Claims (37 CFR 1.16(l))	***	MINUS ****	=	x \$ =		x \$ =		
				Total Additional Fee \$		OR \$		
<small>* If the entry in (D) is less than the entry in (C), Write "0" in column 3.</small> <small>** If the "Highest Number of Total Claims Previously Paid For" is less than 20, Write "20" in this space.</small> <small>*** After any cancellation of claims</small> <small>**** If "A" is greater than 20, use (B - A); If "A" is 20 or less, use (B - 20).</small> <small>***** "Highest Number of Independent Claims Previously Paid For" or Number of Independent Claims in Patent (C).</small>								
<input type="checkbox"/> Please charge Deposit Account No. _____ in the amount of _____. <small>A duplicate copy of this sheet is enclosed.</small>								
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. _____. <small>A duplicate copy of this sheet is enclosed.</small>								
<input checked="" type="checkbox"/> A check in the amount of \$ _____ to cover the filing / additional fee is enclosed.								
 Date <u>9/29/00</u> Signature of Applicant, Attorney or Agent of Record								
Ronald R. Snider <small>Typed or printed name</small>								

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

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## REISSUE PATENT APPLICATION TRANSMITTAL

WITHOUT FEE OR OATH

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09/672146  
09/28/00

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<p><b>Address to:</b>  <b>Assistant Commissioner for Patents</b>  <b>Box Patent Application</b>  <b>Washington, DC 20231</b>  <b>Box: REISSUE</b></p>	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%;">Attorney Docket No.</td> <td style="width: 50%;">IWA-126-USAP</td> </tr> <tr> <td>First Named Inventor</td> <td>Chikao NISHINO</td> </tr> <tr> <td>Original Patent Number</td> <td>5,814,634</td> </tr> <tr> <td>Original Patent Issue Date (Month/Day/Year)</td> <td>09/29/1998</td> </tr> <tr> <td>Express Mail Label No.</td> <td></td> </tr> </table>	Attorney Docket No.	IWA-126-USAP	First Named Inventor	Chikao NISHINO	Original Patent Number	5,814,634	Original Patent Issue Date (Month/Day/Year)	09/29/1998	Express Mail Label No.	
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<b>APPLICATION FOR REISSUE OF:</b> <input checked="" type="checkbox"/> Utility Patent <input type="checkbox"/> Design Patent <input type="checkbox"/> Plant Patent <i>(Check applicable box)</i>											
<b>APPLICATION ELEMENTS</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>1. <input type="checkbox"/> *Fee Transmittal Form (PTO/SB/56) (Submit an original, and a duplicate for fee processing)</p> <p>2. <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.9 and 1.27.</p> <p>3. <input checked="" type="checkbox"/> Specification and Claims (amended, if appropriate)</p> <p>4. <input checked="" type="checkbox"/> Drawing(s) (proposed amendments, if appropriate)</p> <p>5. <input checked="" type="checkbox"/> Reissue Oath/Declaration (original or copy) (37 C.F.R. § 1.175) (PTO/SB/51 or 52) (submitted Original U.S. Patent without signature)</p> <p>6. <input checked="" type="checkbox"/> Offer to Surrender Original Patent (37 C.F.R. § 1.178) (PTO/SB/53 or PTO/SB/54) or <input type="checkbox"/> Ribboned Original Patent Grant <input type="checkbox"/> Statement of Loss (PTO/SB/55)</p> <p>7. Original U.S. Patent currently assigned?  <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  <i>(If Yes, check applicable box(es))</i>  <input type="checkbox"/> Written Consent of all Assignees (PTO/SB/53 or 54)  <input checked="" type="checkbox"/> 37 C.F.R. § 3.73(b) Statement <input type="checkbox"/> Power of Attorney</p> </td> <td style="width: 50%; vertical-align: top;"> <p>8. <input type="checkbox"/> Foreign Priority Claim (35 U.S.C. 119) (if applicable)</p> <p>9. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations</p> <p>10. <input type="checkbox"/> English Translation of Reissue Oath/Declaration (if applicable)</p> <p>11. <input type="checkbox"/> Preliminary Amendment</p> <p>12. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) <i>(Should be specifically itemized)</i></p> <p>13. <input type="checkbox"/> Other: ..... ..... ..... ..... .....</p> </td> </tr> </table>		<p>1. <input type="checkbox"/> *Fee Transmittal Form (PTO/SB/56) (Submit an original, and a duplicate for fee processing)</p> <p>2. <input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.9 and 1.27.</p> <p>3. <input checked="" type="checkbox"/> Specification and Claims (amended, if appropriate)</p> <p>4. <input checked="" type="checkbox"/> Drawing(s) (proposed amendments, if appropriate)</p> <p>5. <input checked="" type="checkbox"/> Reissue Oath/Declaration (original or copy) (37 C.F.R. § 1.175) (PTO/SB/51 or 52) (submitted Original U.S. Patent without signature)</p> <p>6. <input checked="" type="checkbox"/> Offer to Surrender Original Patent (37 C.F.R. § 1.178) (PTO/SB/53 or PTO/SB/54) or <input type="checkbox"/> Ribboned Original Patent Grant <input type="checkbox"/> Statement of Loss (PTO/SB/55)</p> <p>7. Original U.S. Patent currently assigned?  <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No  <i>(If Yes, check applicable box(es))</i>  <input type="checkbox"/> Written Consent of all Assignees (PTO/SB/53 or 54)  <input checked="" type="checkbox"/> 37 C.F.R. § 3.73(b) Statement <input type="checkbox"/> Power of Attorney</p>	<p>8. <input type="checkbox"/> Foreign Priority Claim (35 U.S.C. 119) (if applicable)</p> <p>9. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations</p> <p>10. <input type="checkbox"/> English Translation of Reissue Oath/Declaration (if applicable)</p> <p>11. <input type="checkbox"/> Preliminary Amendment</p> <p>12. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) <i>(Should be specifically itemized)</i></p> <p>13. <input type="checkbox"/> Other: ..... ..... ..... ..... .....</p>								
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### 14. CORRESPONDENCE ADDRESS

<input type="checkbox"/> Customer Number or Bar Code Label			
or <input checked="" type="checkbox"/> Correspondence address below			
<b>Name</b>	Ronald R. Snider		
	Snider & Associates		
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Washington		DC	20036-7613
Country		Telephone	Fax
USA		202-347-2600	202-347-7870

NAME (Print/Type)	Ronald R. Snider	Registration No. (Attorney/Agent)	24,962
Signature			Date
			9/28/2000

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5  
MANUAL OF PATENT EXAMINING PROCEDURE

PTO/SB/56 (12-97)

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JC796 U.S. PTO  
09/672146



09/28/00

**REISSUE APPLICATION FEE TRANSMITTAL FORM**

Docket Number (Optional)

IWA-126-USAP

**Claims as Filed - Part 1**

Claims in Patent	For	Number Filed in Reissue Application	(3) Number Extra	Small Entity		Other than a Small Entity	
				Rate	Fee	Rate	Fee
(A) 26	Total Claims (37 CFR 1.16(j))	(B) 26	**** 6 = x \$ =	or x \$ 18.00	108.00		
(C) 2	Independent Claims (37 CFR 1.16(l))	(D) 2	* = x \$ =				
				Basic Fee (37 CFR 1.16(h))	\$		\$ 690.00
				Total Filing Fee	\$	OR	\$ 798.00

**Claims as Amended - Part 2**

	(1) Claims Remaining After Amendment		(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity		Other than a Small Entity	
					Rate	Fee	Rate	Fee
Total Claims (37 CFR 1.16(j))	***	MINUS	**	*	x \$ =		or x \$ =	
Independent Claims (37 CFR 1.16(l))	***	MINUS	*****	=	x \$ =			
				Total Additional Fee	\$	OR	\$	

\* If the entry in (D) is less than the entry in (C), Write "0" in column 3.

\*\* If the "Highest Number of Total Claims Previously Paid For" is less than 20, Write "20" in this space.

\*\*\* After any cancellation of claims

\*\*\*\* If "A" is greater than 20, use (B -A); If "A" is 20 or less, use (B - 20).

\*\*\*\*\* "Highest Number of Independent Claims Previously Paid For" or Number of Independent Claims in Patent (C).

Please charge Deposit Account No. \_\_\_\_\_ in the amount of \_\_\_\_\_.  
A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. \_\_\_\_\_.  
A duplicate copy of this sheet is enclosed.

A check in the amount of \$ \_\_\_\_\_ to cover the filing / additional fee is enclosed.

9/25/00  
Date

Signature of Applicant, Attorney or Agent of Record

Ronald R. Snider

Typed or printed name

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re Application of: **Chikao Nishino et al.**

Serial No.: (Reissue Application  
of U.S. Patent No. 5,814,634  
issued on September 29, 1998) Art Unit: 1203

Filed: April 17, 1997 Examiner:

For: **Alkylenediamine Derivative, Anti-Ulcer Drug, and  
Antibacterial Drug**

Hon. Assistant Commissioner  
for Patents and Trademarks  
Washington, DC 20231

**REISSUE APPLICATION DECLARATION  
AND POWER OF ATTORNEY BY INVENTORS**

Sir:

We, the named applicants of the above referenced U.S. Patent,  
hereby declare that:

1. Our residences, post office addresses, and citizenships  
are as stated below next to our names.

2. We are the original and joint inventors of the subject  
matter which is described and claimed in U.S. Patent No. 5,814,634  
(hereafter "the '634 patent") granted September 29, 1998, and  
described and claimed in the above-identified reissue application.

3. We have reviewed and understand the contents of the  
specification and claims of the '634 patent and the specification  
and claims of the above-identified reissue application and as  
amended to date.

4. We believe the '634 patent to be wholly or partly  
inoperative or invalid by reason of the patentees claiming less  
than the patentees had the right to claim in said patent and  
because of an error in said patent, which error is described in  
paragraphs 6 through 9 of this Declaration.

5. The errors described in paragraphs 6 through 9 hereof, and all errors being corrected in this reissue application up to the time of filing of this Declaration arose without any deceptive intention on the part of the applicants.

6. During the prosecution of the corresponding European application (Application No. 97 302 666.9; filing date: April 18, 1998) in the European Patent Office (hereafter "the EPO") it was realized that the compounds of claim 1, as originally written, had been inadvertently limited to alkylidendiamine derivatives or salts thereof of a general formula 1 in which "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_3$  and  $R_3'$  is prenyl group or geranyl group, another is methyl group" and that the disclosure of the inventors in the patent was much broader than the scope of the issued claim 1. It was further realized during the prosecution in the EPO, that the compounds of claim 5, as originally written, had been inadvertently limited to alkylidendiamine derivatives or salts thereof of a general formula 4 in which " $R_1$  and/or  $R_2$  is an alkenyloxy group expressed by the...formula 5... wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_b$  and  $R_b'$  is prenyl group or geranyl group, another is methyl group" and that the disclosure of the inventors in the patent was much broader than the scope of the issued claim 5.

7. The error which we seek to cure by reissue is the unintentional omission of one supplementary  $CH_2$  group from (a) the substituents  $R_3$  and  $R_3'$  of claim 1 and (b) the substituents  $R_b$  and

$R_b'$  of claim 5.

8. Amended claim 1 now requires in pertinent part that "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl- $CH_2$  group, or geranyl- $CH_2$  group and when one of  $R_3$  and  $R_3'$  is prenyl- $CH_2$  group or geranyl- $CH_2$  group, another is methyl group," in lieu of the former erroneous proviso reciting that "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_3$  and  $R_3'$  is prenyl group or geranyl group, another is methyl group." Without the proposed amendment, claim 1 provides no coverage for the compounds in which:

- (a)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is  $CH_3-$  and  $R_3'$  is prenyl- $CH_2-$  group when only one neryloxy group is on a benzene ring;
- (b)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is prenyl- $CH_2$  group and  $R_3'$  is methyl group when only one geranyloxy group is on a benzene ring;
- (c)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is geranyl- $CH_2-$  group and  $R_3'$  is methyl group when only one farnesyloxy group is on a benzene ring; and
- (d) one of  $R_1$  and  $R_2$  is geranyloxy,  $R_3$  is prenyl- $CH_2-$  group and  $R_3$  is methyl group when two geranyloxy groups are on a benzene ring.

Such compounds are illustrated in Examples 2-14, 20-26, 29-34, 36-38 and 41-61 of the '634 patent. Thus, this difference is an error related to subject matter which was not previously claimed and, hence, the issued claim 1 does not claim all that we are entitled

to claim in the '634 patent. No new matter is added by this amendment of claim 1.

9. Similarly, amended claim 5 now reads in pertinent part that "wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl- $CH_2$  group, or geranyl- $CH_2$  group and when one of  $R_b$  and  $R_b'$  is prenyl- $CH_2$  group or geranyl- $CH_2$  group, another is methyl group" in lieu of the previous mistaken proviso stating that "wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_b$  and  $R_b'$  is prenyl group or geranyl group, another is methyl group." Without the proposed amendment --because according to the original claim 5  $R_b$  and  $R_b'$  can be neither prenyl- $CH_2$ - group nor geranyl- $CH_2$ - group--claim 5 provides no coverage for the compounds in which each of  $R_1$  and  $R_2$  is alkenyloxy group such as prenyloxy, geranyloxy, neryloxy or farnesylloxy. Such compounds are depicted in Examples 11-14 and 36-38 of the '634 patent. Thus, this difference is an error related to subject matter which was not previously claimed and, hence, the issued claim 5 does not claim all that we are entitled to claim in the '634 patent. No new matter is added by this amendment of claim 5.

10. Support for amended claim 1 that we seek to present in this reissue application can be found in column 17, line 8 through column 21, line 12 (Examples 2-14), column 22, line 31 through column 23, line 33 (Examples 20-26), column 24, line 44 through column 25, line 38 (Examples 29-34), column 27, line 1 through column 23, line 29 (Examples 36-38) and column 29, line 1 through column 23, line 23 (Examples 41-61) of the '634 patent. Similarly,

support for amended claim 5 can be found in column 20, line 34 through column 21, line 12 (Examples 11-14) and column 27-28, line(s) 1 through column 27-28, line(s) 43 (Examples 36-38) thereof. Thus, claims 1 and 5 as proposed to be amended by this reissue recite alkylenediamine derivatives or salts thereof clearly and adequately described in the '634 patent.

11. It was also realized during said prosecution before the EPO, that, in order to obtain broader patent protection, a reissue application needed to be filed no later than September 29, 2000.

12. We acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. 1.56(a) and which occurred between the filing date of said prior application and the filing date of the application which issued as the '634 patent.

13. We hereby claim foreign priority benefits under Section 119 of Title 35, United States Code, of any foreign patent application for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application of which priority is claimed:

- (a) Japanese Patent Application No. 8-122195 filed on Apr. 18, 1996;
- (b) Japanese Patent Application No. 8-278871 filed on Sep. 30, 1996; and
- (c) Japanese Patent Application No. 9-12056 filed on Jan. 6, 1997.

Such priority benefits were claimed in USP 5,814,634, now sought to be reissued. Moreover, the disclosures of the above-identified priority documents were and continue to be incorporated herein by reference.

14. We hereby appoint Ronald R. Snider, Reg. No. 24,962, Elizabeth J. Pawlak, Reg. No. 34,520, Peter N. Lalos, Reg. No., 19,789, Francis A. Keegan, Reg. No. 19,245 to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith. Please direct all telephone calls to: Ronald R. Snider, Esq., at telephone number (202) 347-2600, and all correspondence to:

Snider & Associates  
P.O. Box 27613  
Washington, D.C. 20038-7613

15. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of inventor: Chikao NISHINO

Inventor's signature: Chikao Nishino

Date: October 4, 2000

Citizenship: Japanese

Residence: Yokohama-shi, KANAGAWA, JAPAN

Post Office Address: c/o SHISEIDO RESEARCH CENTER (2)

2-12-1 Fukuura, Kanazawa-ku, Yokohama-shi, KANAGAWA 236, JAPAN



Full name of inventor: Fumitaka SATO

Inventor's signature: Fumitaka Sato

Date: October 4, 2000

Citizenship: Japanese

Residence: Yokohama-shi, KANAGAWA, JAPAN

Post Office Address: c/o SHISEIDO RESEARCH CENTER (1)

1050 Nippa-cho, Kohoku-ku, Yokohama-shi, KANAGAWA 223, JAPAN

Full name of inventor: Tomohiro UETAKE

Inventor's signature: Tomohiro Uetake

Date: October 20, 2000

Citizenship: Japanese

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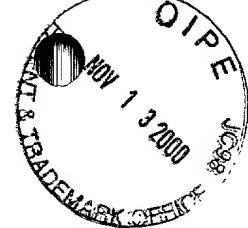
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5-5 Ginza ~~7-chome~~, ~~7-chome~~, Chuo-ku, TOKYO 104-10, JAPAN  
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NOV 13 2000  
398



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Chikao Nishino et al.**

Serial No.: (Reissue Application of U.S. Art Unit: 1203  
Patent No. 5,814,634 issued on  
September 29, 1998)

Filed: April 17, 1997 Examiner:

For: **Alkylenediamine Derivative, Anti-Ulcer Drug, and  
Antibacterial Drug**

Hon. Assistant Commissioner  
for Patents and Trademarks  
Washington, DC 20231

ASSENT OF ASSIGNEE TO REISSUE APPLICATION  
AND  
OFFER TO SURRENDER PATENT

Sir:

Shiseido Co., Ltd. (Tokyo, Japan) (hereinafter "Assignee"), the assignee of the entire interest in U.S. Patent No. 5,814,634, hereby assents to the filing of the above-identified application to reissue said patent.

Further, Assignee hereby offers to surrender said patent in the reissue thereof. As permitted by 37 C.F.R. §1.178, the original of said patent will be submitted in due course upon indication that the application to reissue said patent will be allowed.

Pursuant to 37 C.F.R. § 3.73(b), the Assignee's ownership is established by virtue of an Assignment by all five inventors to the Assignee of their entire interest in the patent, which Assignment was recorded in the U.S. Patent and Trademark Office on April 17, 1997 at Reel 8533, Frame 0020.

Submitted herewith are a copy of said Assignment and a copy of  
the Notice of Recordation of that Assignment.

Respectfully submitted,

Shiseido Co., Ltd. (Tokyo, Japan)

Name in Print: Satoru Takeda

Title: Satoru TAKEDA, General Manager

Date: 24th Oct. 2000



UNITED STATES DEPARTMENT OF COMMERCE

Patent and Trademark Office

ASSISTANT SECRETARY AND COMMISSIONER

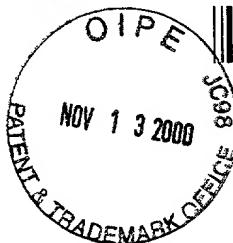
OF PATENTS AND TRADEMARKS

Washington, D.C. 20231

AUGUST 26, 1997

PTAS

RONALD R. SNIDER  
P.O. BOX 27613  
WASHINGTON, D.C. 20038-7613



\*100516403A\*

**CORRECTED  
NOTICE**

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THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE ASSIGNMENT SEARCH ROOM ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

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RECORDATION DATE: 04/17/1997

REEL/FRAME: 8533/0020

NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

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DOC DATE: 04/10/1997

ASSIGNOR:

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DOC DATE: 04/10/1997

ASSIGNOR:

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DOC DATE: 04/10/1997

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DOC DATE: 04/10/1997

ASSIGNOR:

KOJIMA, NAO

DOC DATE: 04/10/1997

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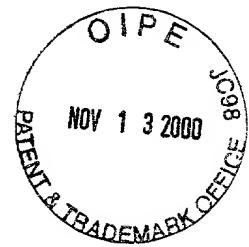
SHISEIDO CO., LTD.  
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8533/0020 PAGE 2

SERIAL NUMBER: 08842891  
PATENT NUMBER:

FILING DATE:  
ISSUE DATE:

JACQUELINE MOORE, PARALEGAL  
ASSIGNMENT DIVISION  
OFFICE OF PUBLIC RECORDS



70990 U.S. PTO  
04/17/97

8-25-1997  
100516403

U.S. DEPARTMENT OF COMMERCE  
VER SHEET Patent and Trademark Office  
Y Atty Dkt No: IWA-126 USA P

61123 U.S. PTO  
08/842891

Commissioner of Patents and Trademarks: Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

1. Chikao NISHINO

Additional name(s) of conveying party(ies) attached?  Yes  No

3. Nature of conveyance:

Assignment

Merger

Security Agreement

Change of Name

Other:

Execution Date: April 10, 1997

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: April 10, 1997

A. Patent Application No.(s)

\*

Additional numbers attached?  Yes  No

5. Name and address of party to whom correspondence concerning document should be mailed:

Ronald R. Snider  
P.O. Box 27613  
Washington, D.C. 20038-7613  
(202) 347-2600  
6/1997 INASHI 0000010 08842891  
C:381 40.00 OP

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): \$40.00

Enclosed

Authorized to be charged to deposit account if any error.

8. Deposit account number:  
19-2816

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Ronald R. Snider  
Name of Person Signing  
Registration No. 24,962

Signature

April 17, 1997  
Date

Total number of pages comprising cover sheet, attachments and document: 3

Mail documents to be recorded with required cover sheet information to:  
Commissioner of Patents and Trademarks  
Box Assignments  
Washington, D.C. 20231

**ADDITIONAL NAMES OF CONVEYING PARTIES**

2. Fumitaka SATO
3. Tomohiro UETAKE
4. Hirotada FUKUNISHI
5. Nao KOJIMA

## ASSIGNMENT

SOLE/JOINT INVENTION  
(U.S. Rights Only)

IWA-126

WHEREAS I/We, the below named inventor(s), [hereinafter referred to as Assignor(s)], have made an invention entitled:  
ALKYLENDIAMINE DERIVATIVE, ANTI-ULCER DRUG, AND ANTIBACTERIAL DRUG

(Title of Invention)

for which I/We executed an application for United States Letters Patent concurrently herewith or filed an application for United States Letters Patent on \_\_\_\_\_, 19 \_\_\_\_ (Serial No. \_\_\_\_\_); and  
WHEREAS, \_\_\_\_\_

(Full Name of Assignee)

a corporation of JAPAN

(Country of Incorporation)

whose post office address is 5-5 Ginza 7-chome, Chuo-ku, TOKYO 104-10 JAPAN

(hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention, the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that, for good and valuable consideration the receipt of which from assignee is hereby acknowledged, I/We, as assignor(s), have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the assignee, its lawful successors and assigns, my/our entire right, title, and interest in and to this invention and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States which may be granted thereon, and all reissues thereof; and I/We hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue all Letters Patent for this invention to assignee, its successors and assigns, in accordance with the terms of this Assignment:

AND, I/WE HEREBY further covenant and agree that I/We will, without further consideration, communicate with assignee, its successors and assigns, any facts known to me/us respecting this invention and testify in any legal proceeding, sign all lawful papers when called upon to do so, execute and deliver all papers that may be necessary or desirable to perfect the title to this invention in said assignee, its successors and assigns, execute all divisional, continuation, and reissue applications, make all rightful oaths and generally do everything possible to aid assignee, its successors and assigns, to obtain and enforce proper patent protection for this invention in the United States, it being understood that any expense incident to the execution of such papers shall be borne by the assignee, its successors and assigns.

IN TESTIMONY WHEREOF, I/We have hereunto set our hand(s).

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ADDRESS	CITIZENSHIP	

September 28, 2000

DOCKET NO.: IWA-126-USA-P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Chikao Nishino et al.

Serial No.: Reissue Application of Art Unit: 1203  
US Patent No. 5,814,634  
issued on September 29, 1998

Filed: April 17, 1997 Examiner: Covington, R.

For: Alkylenediamine Derivative, Anti-Ulcer Drug, and  
Antibacterial Drug

STATEMENT UNDER 37 C.F.R. § 3.73(B)

ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

Attached hereto is a copy of the executed assignment which was submitted for recording and a copy of the Corrected Notice of Recordation specifying the reel and frame number. I hereby state that these papers show that Shiseido Co., Ltd. is the Assignee of the above captioned patent. I am the Attorney of Record in the prosecution of the original patent application, serial number 08/842,891, and I am the Attorney of Record in the reissue application filed on September 28, 2000. I am authorized act on behalf of the Assignee.

Respectfully submitted,



Ronald R. Snider  
Reg. No. 24,962

Date: September 28, 2000

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RRS/bam

## 1

# ALKYLENEDIAMINE DERIVATIVE ANTI- ULCER DRUG AND ANTIBACTERIAL DRUG

## RELATED APPLICATIONS

This application claims the priority of Japanese Patent Application No. 8-122195 filed on Apr. 18, 1996. Japanese Patent Application No. 8-278871 filed on Sep. 30, 1996. Japanese Patent Application No. 9-12056 filed on Jan. 6, 1997, which are incorporated herein by references.

## FIELD OF THE INVENTION

The present invention relates to an alkylenediamine derivative and, in particular, to an alkylenediamine derivative having an antibacterial activity against *Helicobacter pylori* or an anti-ulcer effect.

## BACKGROUND OF THE INVENTION

Various theories have been proposed with respect to a cause of ulcer in human. In particular, it has been elucidated that stress, taking of non-steroidal anti-inflammatory drugs for curing rheumatic diseases, and the like are closely related to ulcer formation, mainly due to relatively excess gastric acid secretion. Accordingly, it is important to suppress the acid secretion in order to prevent ulcer formation and to cure it.

On the other hand, it has been considered that *Helicobacter pylori*, which is a rod normally existing in stomach, generates ammonia due to its strong urease activity, thereby inducing ulcer and persistence of itself. Since it persistently lives within mucus and mucosa, it becomes the greatest cause for recurrence of ulcer. Accordingly, it has been considered that the recurrence of ulcer can be prevented if this bacterium is sterilized.

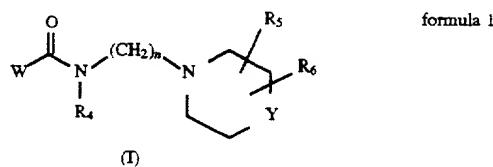
Though various kinds of medicaments for curing ulcer have been conventionally developed, few medicaments have been known to have an effect for preventing stress ulcers from generating and an antibacterial activity against *Helicobacter pylori*.

## DISCLOSURE OF THE INVENTION

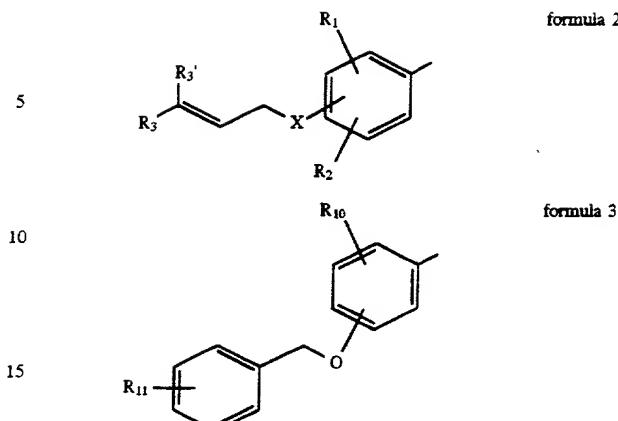
In view of the problems of the above-mentioned prior art, the object of the present invention is to provide a compound which is excellent in preventing ulcer from generating and to provide antibacterial drug against *Helicobacter pylori* and anti-ulcer drug including such a compound as a main component.

As a result of the diligent studies conducted by the inventors, it has been found that a specific alkylenediamine derivative is effective against various kinds of ulcer due to its antibacterial property against *Helicobacter pylori* or its acid secretion inhibition as a main action mechanism. Thus, the present invention has been accomplished.

Namely, an alkylenediamine derivative or a salt thereof in accordance with the present invention is expressed by the following formula 1:



wherein W represents a group expressed by the following formula 2 or formula 3;



wherein each of  $R_1$  and  $R_2$  represents hydrogen atom, a lower alkoxy group, an alkenyloxy group, or a halogen atom;

each of  $R_3$  and  $R_3'$  represents methyl group, [prenyl] prenyl-CH<sub>2</sub> group, or [geranyl] geranyl-CH<sub>2</sub> group and when one of  $R_3$  and  $R_3'$  is [prenyl] prenyl-CH<sub>2</sub> group or [geranyl] geranyl-CH<sub>2</sub> group, another is methyl group;

25      X represents oxygen atom or sulfur atom;  
 R<sub>10</sub> represents a lower alkyl group; and  
 R<sub>11</sub> represents a halogen atom; and wherein each of R<sub>4</sub>,  
 R<sub>5</sub>, and R<sub>6</sub> represents hydrogen atom or a lower alkyl group;  
 30      Y represents a group expressed by —CH<sub>2</sub>—, —O—, or  
 —N(R<sub>7</sub>)—, while R<sub>7</sub> represents a lower alkyl group, an aryl group, a carbamoyl lower alkyl group, an aralkyl group, or a heterocyclic group having 5 to 9 members;  
 and  
 n represents an integer of 1 to 6.

35      An anti-ulcer drug in accordance with the present invention comprises, as an effective ingredient, said alkylenediamine derivative or the pharmacologically acceptable salt thereof, together with a pharmaceutically acceptable carrier and/or adjuvant.

40      An antibacterial drug against *Helicobacter pylori* in accordance with the present invention comprises, as an effective ingredient, said alkylenediamine derivative or the pharmacologically acceptable salt thereof, together with a pharmaceutically acceptable carrier and/or adjuvant

45      A method for the treatment of peptic ulcers in man or mammals in accordance with the present invention comprises administering an effective amount of said alkylenediamine derivative or the pharmacologically acceptable salt thereof to a host.

50      A method for the inhibition of acid secretion in stomach of man or mammals in accordance with the present invention comprises administering an effective amount of said alkylenediamine derivative or the pharmacologically acceptable salt thereof to a host.

55      A method for the inhibition of growth of *Helicobacter pylori* in stomach of man or mammals in accordance with the present invention comprises administering an effective amount of said alkylenediamine derivative or the pharmacologically acceptable salt thereof to a host.

60      A method for the prevention of peptic ulcers in man or mammals in accordance with the present invention comprises administering an effective amount of said alkylenediamine derivative or the pharmacologically acceptable salt thereof to a host.

#### BRIEF DESCRIPTION OF THE DRAWINGS

65      FIG. 1 shows an example of a step for manufacturing the alkylenediamine derivative in accordance with the present invention and

### 3

FIGS. 2 to 7 show examples of steps for manufacturing material compounds for the alkylidendiamine derivative in accordance with the present invention.

#### EXAMPLES

In the compound in accordance with the present invention, the lower alkoxy group found at  $R_1$  and  $R_2$  is a straight or branched alkoxy group having 1 to 6 carbon atoms. Examples thereof include methoxy, ethoxy, n-propyloxy, n-butyloxy, isopropyloxy, isobutyloxy, 1-methylpropyloxy, tert-butyloxy, n-pentyloxy, 1-ethylpropyloxy, isoamyoxy, and n-hexyloxy group. Preferably, they are methoxy groups.

The alkenyl group of "alkenyloxy group" found at  $R_1$  and  $R_2$  represents a straight or branched alkenyl group which has at least one double bond and has 2 to 20 carbon atoms. While the double bond has two kinds of configurations, namely, cis and trans, each double bond in alkenyl group may have either configurations. It is preferably a branched alkenyl group from the viewpoint of effect. Particularly, prenyl group, geranyl group, neryl group or farnesyl group is preferable.

In the present invention, each of  $R_1$  and  $R_2$ , which may be identical to or different from each other, can be hydrogen atom, said lower alkoxy group, said alkenyloxy group, or a halogen atom.

The lower alkyl group found at  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ , and  $R_{10}$  is a straight or branched alkyl group having 1 to 8 carbon atoms. Examples thereof include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl, n-hexyl, and 2-ethylhexyl group. A preferable example of  $R_4$  is ethyl group. A preferable example of  $R_5$  and  $R_6$  is methyl group. A preferable example of  $R_7$  is ethyl or isobutyl group. A preferable example of  $R_{10}$  is isobutyl group.

Each of  $R_4$ ,  $R_5$ , and  $R_6$ , which may be identical to or different from each other, can be hydrogen atom said lower alkyl group.

$R_7$  can be the said lower alkyl group, an aryl group, a carbamoyl lower alkyl group, an aralkyl group, or an unsaturated heterocyclic group having 5 to 9 members.

Examples of the aryl group found at  $R_7$  include phenyl group and naphtyl group. A preferable example thereof is phenyl group. Also, the aryl group can have a substituted group on its aromatic ring. Examples of such a substituted group include a lower alkoxy group. Here, the lower alkoxy group is defined as above and is preferably methoxy group.

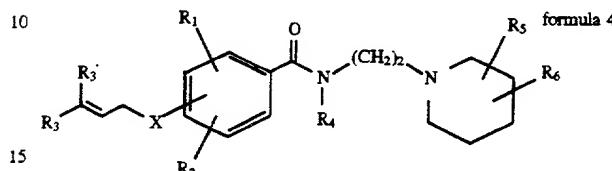
The carbamoyl lower alkyl group found at  $R_7$  represents a group in which a hydrogen atom of a lower alkyl group is substituted by a carbamoyl group—CONH<sub>2</sub>. Here, the lower alkyl group is defined as above. A preferable example thereof is a straight lower alkyl group and, particularly, methyl group. Also, the hydrogen atom of the carbamoyl group can be substituted by a lower alkyl group. Such a lower alkyl group can be exemplified by the above-mentioned lower alkyl group and is preferably isopropyl group. Also, the nitrogen atom of the carbamoyl group can be a member of a saturated heterocyclic group to form it. A preferable example of such a heterocyclic group is pyrrolidino group.

Examples of the aralkyl group found at  $R_7$  include benzyl group and phenethyl group. A preferable example thereof is benzyl group. Also, the aralkyl group can have a substituted group on its aromatic ring. Examples of such a substituted group include a halogen atom and a methylenedioxy group.

Preferably examples of such a substituted aralkyl group are fluorobenzyl group and 3,4-methylenedioxybenzyl group.

Examples of the unsaturated heterocyclic group having 5 to 9 members found at R<sub>7</sub> include a group contained nitrogen and/or oxygen atom. Preferable examples thereof are thiazolyl, benzothiazolyl, and pyrimidinyl group.

A preferable compound of the present invention may be expressed by the following formula 4:

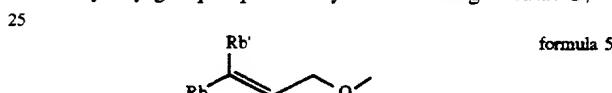


wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and X are same as those in the above mentioned formula 1.

In formula 4, it is preferable that X is oxygen atom, while R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen atoms.

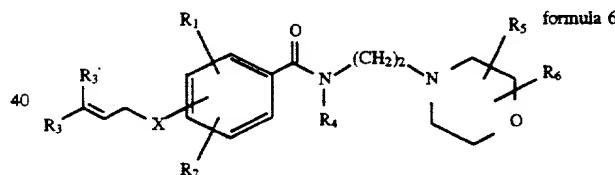
In formula 4, it is preferable that R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

In formula 4, it is preferable that R<sub>1</sub> and/or R<sub>2</sub> is an alkenyloxy group expressed by the following formula 5;



wherein each of R<sub>b</sub> and R<sub>b</sub>' represents methyl group, [prenyl] prenyl-CH<sub>2</sub> group, or [geranyl] geranyl-CH<sub>2</sub> group and when one of R<sub>b</sub> and R<sub>b</sub>' is [prenyl] prenyl-CH<sub>2</sub> group or [geranyl] geranyl-CH<sub>2</sub> group, another is methyl group.

A preferable compound of the present invention may be expressed by the following formula 6:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>', R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and X are same as those in the above-mentioned formula 1.

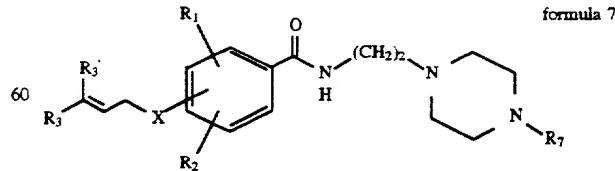
In formula 6, it is preferable that X is oxygen atom, while R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen atoms.

In formula 6, it is preferable that R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

In formula 6, it is preferable that R<sub>1</sub> and/or R<sub>2</sub> is an alkenyloxy group expressed by above-mentioned formula 5.

In formula 6, it is preferable that R<sub>1</sub> and/or R<sub>2</sub> is a lower alkoxy group.

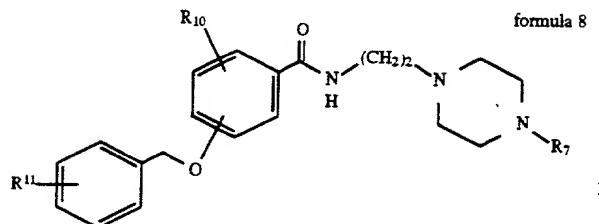
A preferable compound of the present invention may be expressed by the following formula 7:



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3</sub>', R<sub>7</sub>, and X are same as those in the above-mentioned formula 1.

In formula 7, it is preferable that X is oxygen atom, while R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

A preferable compound of the present invention may be expressed by the following formula 8:



wherein R<sub>7</sub> is a lower alkyl group; and R<sub>10</sub> and R<sub>11</sub> are same as those in the above-mentioned formula 3.

In formula 8, it is preferable that R<sub>7</sub> and R<sub>10</sub> are isobutyl groups.

In formula 8, it is preferable that R<sub>11</sub> is fluorine atom bonded to para-position.

The alkylendiamine derivatives and its pharmacologically acceptable salts in accordance with the present invention have anti-ulcer effect, acid secretion inhibition effect, and anti-bacterial effect against *Helicobacter pylori* as well as a high safety. Accordingly, they are useful as medicaments for preventing and curing various kinds ulcer.

As similar compounds to the present invention, there have been known an alkylendiamine derivative having an analgesic action and spasmolysis effect in stomach and bowel in Japanese Examined Patent Publication No. 40-19344, an alkylendiamine derivative having a gastric movement accelerating effect and an emesis effect in Japanese Unexamined Patent Publication No. 1-168678, an alkylendiamine derivative having an enterokinesis accelerating effect in Japanese Unexamined Patent Publication No. 2-207069, and an alkylendiamine derivative having a cerebrovascular damage ameliorating effect in Japanese Unexamined Patent Publication No. 5-239005. However, all of them do not relate to the pharmacological effect of the present invention. Also, the alkylendiamine derivative in accordance with the present invention is characterized in that W in the basic skeleton of formula 1 is a phenyl group having 1 to 3 alkenyloxy groups on its aromatic ring as shown in formula 2, or a phenyl group having both of a benzyloxy group and a lower alkyl group on its aromatic ring as shown in formula 3. Such an alkylendiamine derivative has not been known even from the viewpoint of structure. Accordingly, the alkylendiamine derivative of the present invention is a novel compound completely.

In the following, while the general method for manufacturing the compound of the present invention will be explained, it should not be restricted thereto.

The compound(I) of the present invention expressed by formula 1 can be manufactured by reaction formula A shown in FIG. 1.

In reaction formula A, the alkylendiamine derivative(I) of the present invention can be obtained from a carboxylic acid(II) and an amine(III) by using a known amide-bond forming reaction such as mixed anhydride method, acid chloride method, DCC method, CDI method, or azide method. Here, W in the compound(II), and R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, n, and Y in the compound (III) are defined as formula 1 mentioned above.

In the mixed anhydride method, by using an activator such as diphenyl phosphinic chloride, ethyl chloroformate, isobutyl chloroformate, or pivaloyl chloride, the carboxylic acid (II) is converted into its corresponding anhydride and then reacted with the compound(III). As an additive, for example, an organic base such as triethyl amine, pyridine, or N-methylmorpholine can be used. As a solvent, for example,

a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic hydrocarbon such as benzene, toluene, or xylene; an ether such as tetrahydrofuran or dioxane; or an amide such as dimethylformamide or dimethylacetamide can be used. While the reaction temperature and reaction time may be changed according to the material compounds used, the reaction is usually effected at a temperature within the range of  $-15^{\circ}\text{ C.}$  to the reflux temperature of the solvent.

In the acid chloride method, as an activator, for example, phosphorus pentachloride, phosphorus trichloride, or thionyl chloride is used to convert the carboxylic acid (II) into the corresponding acid chloride and then the latter is reacted with the compound (III). As an additive, for example, an organic base such as triethyl amine, pyridine, or 5 N-methylmorpholine can be used. As a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic hydrocarbon such as benzene, toluene, or xylene; or an amide such as dimethyl formamide or dimethylacetamide can be used. While the reaction temperature and reaction time may be changed according to the material compounds used, the reaction is usually effected at a temperature within the range of  $0^{\circ}\text{ C.}$  to the reflux temperature of the solvent.

In the DCC method, as a condensing agent, for example, 25 dicyclohexyl carbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCl) can be used. As a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic hydrocarbon such as benzene, toluene, or xylene; an ether such as tetrahydrofuran or dioxane; or an amide 30 such as dimethylformamide or dimethylacetamide can be used. If necessary, this reaction may be effected while 1-hydroxybenzotriazole (HOBt) or N-hydroxy succinimide (HOSu) is added thereto. While the reaction temperature and reaction time may be changed according to the material 35 compounds used, the reaction is usually effected at a temperature within the range of  $0^{\circ}\text{ C.}$  to the reflux temperature of the solvent.

In the CDI method, as an activator, for example, N,N'-carbonyldiimidazole is used to convert the carboxylic acid 40 (II) into the corresponding N-acyl derivative and then the latter is reacted with the compound(III). As an additive, for example, an organic base such as triethylamine, pyridine, or N-methylmorpholine or an inorganic base such as sodium hydride or potassium hydride can be used. As a solvent, for 45 example, a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic hydrocarbon such as benzene, toluene, or xylene; an ether such as tetrahydrofuran or dioxane; or an amide such as dimethylformamide or dimethylacetamide can be used. While the reaction temperature and reaction time may be changed according to the material 50 compounds used, the reaction is usually effected at a temperature within the range of  $0^{\circ}\text{ C.}$  to the reflux temperature of the solvent.

In the azide method, as an activator, for example, diphenylphosphorylazide is used to convert the carboxylic acid 55 (II) into the corresponding azide and then the latter is reacted with the compound (III). As an additive, for example, an organic base such as triethylamine, pyridine, or N-methylmorpholine is used. As a solvent, for example, a 60 halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic hydrocarbon such as benzene, toluene, or xylene; an ether such as tetrahydrofuran or dioxane; or an amide such as dimethylformamide or dimethylacetamide can be used. While the reaction temperature and reaction 65 time may be changed according to the material compounds used, the reaction is usually effected at a temperature within the range of  $0^{\circ}\text{ C.}$  to the reflux temperature of the solvent.

Specifically, for example, diphenylphosphinic chloride or pivaloyl chloride is used as an activator for the mixed anhydride method, while triethylamine is used as an additive to effect a reaction in a solvent such as chloroform or dimethyl formamide at a temperature within the range of -15° C. to room temperature, thereby attaining the aimed object.

Among the material compound(II) used in reaction formula A, the compound (II-a) wherein W is a group expressed by formula 2 can be synthesized by reaction formula B shown in FIG. 2, for example.

In reaction formula B, m in the compound (IV) represents an integer of 1 to 3. While R<sub>1</sub>, R<sub>2</sub>, and X are defined as formula 2 mentioned above, R<sub>1</sub>=H when m=2, and R<sub>1</sub>=R<sub>2</sub>=H when m=3. Ra represents a carboxyl-protecting group which may be a lower alkyl group such as methyl group, ethyl group, or tert-butyl group, phenacyl group, or trichloroethyl group as long as no problem occurs in the subsequent reaction. Z in the compound (V) represents a halogen atom. R<sub>3</sub> and R<sub>3</sub>' are defined as formula 2 mentioned above.

In reaction formula B, an alkenyl halide(V) is reacted with a compound(IV) in the presence of a base and then hydrolyzed so as to synthesize the carboxylic acid (II-a).

The first step of this reaction can be effected in the presence of a base. Sodium amide, triethylamine, sodium hydride, sodium hydroxide, potassium carbonate, barium oxide, silver oxide, or the like can be used therefor. Also, a catalytic amount of potassium iodide can be added thereto. As a solvent, for example, an alcohol such as methanol, ethanol, or butanol; an aromatic compound such as benzene, toluene, xylene, or pyridine; an ether such as diethylether, tetrahydrofuran, or dioxane; an amide such as dimethylformamide or dimethylacetamide; or a ketone such as dimethylsulfoxide or acetone can be used. While the reaction temperature and reaction time may be changed according to the material compounds used, the reaction is usually effected at a temperature within the range of 0° C. to the reflux temperature of the solvent.

Specifically, for example, the compound (IV) is dissolved in tetrahydrofuran or N,N-dimethylformamide and, after sodium hydride is added as a base and stirred therein, the alkenyl halide(V) is added thereto so as to effect a reaction at a temperature within the range of room temperature to the reflux temperature of the solvent, thereby attaining the aimed object.

In the reaction of the second step, the ester compound (VI) is hydrolyzed in the presence of an acid or a base so as to synthesize the carboxylic acid (II-a). Hydrochloric acid, sulfuric acid, p-toluenesulfonic acid, or the like can be used as the acid, while sodium hydroxide, potassium hydroxide, potassium t-butoxide, or the like can be used as a base. As a solvent, a carboxylic acid such as formic acid or acetic acid, an alcohol such as methanol or ethanol; water; or a mixed solvent thereof can be used. While the reaction temperature and reaction time can be changed according to the material compounds used, the reaction is usually effected at a temperature within the range of 0° C. to the reflux temperature of the solvent.

Specifically, for example, the ester compound(VI) is dissolved in an alcohol such as methanol or ethanol and then an aqueous sodium hydroxide or potassium hydroxide solution is added thereto so as to effect a reaction at a temperature within the range of room temperature to reflux temperature of the solvent, thereby attaining the aimed object.

The material compound (V) used in reaction formula B can be synthesized by reaction formula C shown in FIG. 3.

In reaction formula C, Z,  $R_3$ , and  $R_3'$  are defined as those in reaction formula B mentioned above. In this reaction formula, an alkenyl halide (V) can be obtained by halogenation of alcohol (VII).

5 For this reaction, a general method known as halogenation of hydroxy groups can be used. As a reagent of halogenation, for example, a strong acid such as hydrochloric acid or hydrobromic acid; a phosphorus compound such as phosphorus tribromide, phosphorus trichloride, or phosphorus pentachloride; thionyl chloride;

10  $N$ -halogenosuccinimide and methyl sulfide; triphenylphosphine and a halogenated hydrocarbon; or methanesulfonyl chloride and lithium halide is used to effect the reaction. As a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic compound

15 such as benzene, toluene, xylene, or pyridine; an ether such as diethylether, tetrahydrofuran or dioxane; or an amide such as  $N,N$ -dimethylformamide or  $N,N$ -dimethylacetamide can be used. While the reaction temperature and reaction time may be changed according to the material compounds used.

20 the reaction is usually effected at a temperature within the range of 0° C. to the reflux temperature of the solvent.

Specifically, for example, in the presence of lithium chloride and triethylamine, methanesulfonyl chloride is used so as to effect a reaction in a solvent such as acetone at a 25 temperature within the range of 0° C. to room temperature, thereby attaining the aimed object.

Among material compounds(II) used in reaction formula A, the compound (II-b) wherein W is a group expressed by formula 3 above-mentioned can be synthesized according to 30 reaction formula D shown in FIG. 3, for example.

At the first step of reaction formula D, the compound (XVII) is reacted with the substituted benzyl halide(XVIII) in the presence of a base to obtain the compound (XIX).  $R_{10}$  in the compound (XVII), and  $R_{11}$  in the compound (VIII) are 35 defined as those of formula 3 mentioned above, while Z in the compound (XVIII) represents a halogen atom. Ra in the compound (XVII) represents a carboxyl-protecting group which may be a lower alkyl group such as methyl group, ethyl group, or tert-butyl group, phenacyl group, or trichloroethyl group as long as no problem occurs in the subsequent 40 reaction.

As a base in this reaction, for example, an inorganic base such as potassium carbonate, potassium hydroxide, sodium 45 hydroxide, or sodium hydride; or an organic base such as triethylamine or pyridine can be used. Specifically, for example, potassium carbonate is used as a base so as to effect a reaction in a solvent such as acetone or  $N,N$ -dimethylformamide at a temperature within the range of room temperature to the reflux temperature of the solvent, thereby attaining the aimed object.

At the second step of reaction formula D, the compound (XIX) is subjected to a deprotecting reaction so as to obtain the carboxylic acid(II-b).

For this deprotecting reaction, various kinds of known 55 methods can be used according to the kind of the protecting group Ra. For example, when Ra is methyl or ethyl group, known ester hydrolysis method is used for deprotection. Specifically, for example, an inorganic base such as sodium hydroxide or potassium hydroxide is used so as to effect a 60 reaction in a solvent such as water, methanol, or ethanol at a temperature within the range of room temperature to the reflux temperature of the solvent, thereby attaining the aimed object.

On the other hand, among the material compounds(III) 65 used in reaction formula A, for example, the compound (III-a) wherein  $n=2$  and  $R_4=H$  can be synthesized according to reaction formula E shown in FIG. 5.

In reaction formula E. a halogenoacetonitrile (IX) is reacted with an amine (VIII) in the presence of a base and then the cyano group is reduced so as to synthesize the ethylenediamine (III-a). Here, in the compound (VIII). R<sub>5</sub>, R<sub>6</sub>, and Y are defined as those in formula 1. Z in the compound (IX) represents a halogen atom.

At the first step of this reaction, the reaction can be effected under a reaction condition similar to that of the first step in reaction formula B.

For reduction of the cyano group at the second step in this reaction, a known method can be used. For example, Birch reduction method, a reduction method by a metal hydride complex compound, or a method using Raney nickel can be used. In Birch reduction, while sodium or lithium is used mainly as a catalyst, the reaction can be effected in the mixed solvent of liquid ammonia and an alcohol such as methanol or ethanol. When the metal hydride complex compound is used, lithium aluminium hydride, aluminium hydride, sodium borohydride, or the like can be used as a reagent. As a solvent, for example, an ether such as diethylether, tetrahydrofuran or dioxane; or an alcohol such as methanol, ethanol, or butanol can be used. When sodium borohydride is used, Raney nickel, aluminium chloride, cobalt chloride, or the like can be used as a catalyst. When Raney nickel is used, methanol saturated by ammonia is used as a solvent so as to effect hydrogenation under a pressure, thereby attaining the aimed object. While the reaction temperature and reaction time may be changed according to the material compounds used in all cases, the reaction is usually effected at a temperature within the range of 0° C. to the reflux temperature of the solvent.

Specifically, for example, lithium aluminium hydride is suspended in tetrahydrofuran while being cooled with ice and, after the compound (X) is dropped thereto, the reaction is effected at a temperature within the range of 0° C. to the reflux temperature of the solvent. Then, the reaction solution is treated with water, an aqueous sodium hydroxide solution, or the like, thereby attaining the aimed object.

Also, among the material compound(III) used in reaction formula A. the compound(III-b) wherein n=2 and R<sub>4</sub> is a lower alkyl group can be synthesized according to reaction formula F shown in FIG. 6.

In reaction formula F, ethylenediamine (III-a) is amidated with the compound (XI) and then the ketone group in the amide bond is reduced so as to synthesize the ethylenediamine (III-b). Here, in the compound (III-a), R<sub>5</sub>, R<sub>6</sub> and Y are defined as those in formula 1 mentioned above. In the compound (XI), R<sub>8</sub> represents hydrogen atom or a lower alkyl group, while A represents hydroxy group or —OCOR<sub>8</sub>.

The amidation at the first step of this reaction can be effected under a reaction condition similar to that in reaction formula A.

In the reaction at the second step, as a reducing reagent, for example, lithium aluminium hydride, aluminium hydride, or sodium borohydride and triethyloxonium tetrafluoroborate can be used. As a solvent, for example, a halogenated hydrocarbon such as dichloromethane or chloroform; an aromatic compound such as benzene, toluene, xylene, or pyridine; an alcohol such as methanol, ethanol, or butanol; or an ether such as diethylether, tetrahydrofuran or dioxane can be used. While the reaction temperature and reaction time may be changed according to the material compounds used in all cases, the reaction is usually effected at a temperature within the range of 0° C. to the reflux temperature of the solvent.

Specifically, for example, lithium aluminium hydride is suspended in tetrahydrofuran while being cooled with ice

## 10

and, after the amide compound (XII) is dropped thereto, the reaction is effected at a temperature within the range of 0° C. to the reflux temperature of the solvent. Then, the reaction solution is treated with water, an aqueous sodium hydroxide solution, or the like, thereby attaining the aimed object.

Among the material compound(VIII) used in reaction formula E mentioned above, the compound (XVI) wherein Y is a group expressed by  $-\text{N}(\text{R}_7)-$  can be synthesized according to reaction formula G shown in FIG. 7.

- 10 In reaction formula G,  $\text{R}_9$  in the compound (XIII) represents an amino-protecting group which can be a urethane type protecting group such as benzylloxycarbonyl group or tert-butyloxycarbonyl group, an acyl type protecting group such as formyl group or tosyl group, or an alkyl type protecting group such as trityl group as long as no problem occurs in the subsequent reaction.  $\text{R}_5$  and  $\text{R}_6$  in the compound (XIII), and  $\text{R}_7$  in the compound (XIV) are defined as those in formula 1 mentioned above, while Z represents a halogen atom.
- 20 At the first step of reaction formula G, the protected piperazine (XIII) is reacted with an appropriate halide (XIV) in the presence of a base so as to obtain the compound (XV). This reaction can be effected under a reaction condition similar to that of the first step in reaction formula B.
- 25 At the second step of reaction formula G, the compound (XV) is subjected to a deprotecting reaction so as to obtain the compound (XVI). For this deprotecting reaction, various kinds of known methods can be used according to the kind of the amino-protecting group  $\text{R}_9$ . For example, hydrazine, hydrochloric acid, hydrogen peroxide, or the like can be used as the deprotecting agent when  $\text{R}_5$  is formyl group. Specifically, for example, hydrochloric acid within the range of 1N to 6N is used to effect the reaction in methanol at a temperature within 0° C. to room temperature, thereby attaining the aimed object.

Among the material compounds used in the above-mentioned reaction formulas A to G, those with no preparation methods described may be commercially available or easily synthesized by using a known method.

- 30 40 Also, examples of salts of the alkylenediamine derivative of the present invention (I) with an acid include salts with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid and salts with organic acids such as acetic acid, propionic acid, citric acid, lactic acid, oxalic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, and methane sulfonic acid. These salts can be easily manufactured by a normal method.

The alkylenediamine derivative in accordance with the present invention has a strong effect against stress ulcer and an excellent effect for suppressing gastric acid secretion. Furthermore, it has an antibacterial activity against *Helicobacter pylori* which is supposed to be a cause for recurrence of ulcer. Accordingly, it is useful as a medicament for curing and preventing peptic ulcer in man or mammals and, particularly, gastric ulcer in man. Conventionally, there has hardly been known such a compound which has both effect for suppressing gastric acid secretion and antibacterial activity against *Helicobacter pylori*. Accordingly, it is indicated that the compound of the present invention is not only effective in preventing and curing ulcer but also in preventing the recurrence thereof.

When the compound of the present invention is administered as a medicament for curing and preventing peptic ulcer, it may be administered orally as tablet, powder, granule, capsule, syrup, or the like as well as parenterally as suppository, injection, external drug, instillation or the like. While the amount of administration may be outside of the

range mentioned below according to the degree of symptom, personal difference, age, kind of ulcer, or the like, it should of course be adjusted so as to fit the individual circumstances in specific cases. Usually 0.01 to 200 mg/kg or, preferably, 0.05 to 50 mg/kg or, more preferably, 0.1 to 10 mg/kg is administered per day for an adult in a single dose or several doses.

When formulating the medicament, a normal manufacturing method is used with a normal formulation carrier. If necessary, pharmacologically and pharmaceutically acceptable additives may be added thereto.

Namely, when preparing an oral solid formulation, after an excipient and, if necessary, a binder, a decaying agent, a luster, a coloring agent, a correctives, and the like are added to the main medicament, a normal method is used to form tablet, coated tablet, granule, powder, capsule, or the like.

Examples of the excipient include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose, and silicon dioxide. Examples of the binder include polyvinylalcohol, polyvinylether, ethyl cellulose, methyl cellulose, gum arabic, tragacanth, gelatin, shellac, hydroxypropyl cellulose, hydroxypropyl starch, and polyvinylpyrrolidone. Examples of the decaying agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, and pectin. Examples of the luster include magnesium stearate, talc, polyethyleneglycol, silica, and hardened vegetable oil. As the coloring agent, those permitted to be added to medicines are used. Examples of the correctives include cocoa powder, menthol, aromatic acid, mentha oil, borneol, and cinnamon powder. If necessary, these tablet and granule can be coated with sugar-coating, gelatin-coating, and the like.

When preparing an injection, if necessary, a pH-adjusting agent, a buffer, a stabilizer, a solubilizer, and the like are added to the main medicament and then a normal method is used to form subcutaneous, intramuscular, and intravenous injection drugs.

In the following, the present invention will be explained in further detail by specifically examples. However, the present invention should not be restricted to these examples.

First, test methods used for evaluating these examples will be explained.

#### WIS: Restraint and Water Immersion Stress-Induced Ulcer Inhibition Test

##### i) Meaning

The degree of inhibition of the stress ulcer formation is tested.

##### ii) Method

Male Crj:SD or Slc:SD rats (6 to 7-week-old) were fasted overnight, but allowed free access to water. Each group has 5 to 8 of these rats. The sample compound was dissolved or suspended in an aqueous solution of 0.3% sodium carboxymethylcellulose or 0.05% Tween 80 and then was orally administered (100 mg/10 ml/kg). To a control group, the vehicle was administered. 10 minutes later, the rats were placed in a stress cage and immersed to the level of xiploid process in a water bath (21° C.) for 7 hours. At the end of the stress, the rats were sacrificed by inhalation of ether or carbon dioxide. Then, the stomach of each was removed, inflated by injecting 10 ml of 5% formalin neutral buffer solution, and immersed in 1% formalin neutral buffer solution for 30 minutes or more to be fixed. The stomach was incised along the greater curvature and then the length of each erosion in the glandular portion was determined under dissecting microscope. The sum of the length of erosions per stomach was defined as ulcer index (UI).

## iii) Judgment Standard

The effect obtained when 100 mg/kg of the sample compound had been administered was expressed as ulcer formation inhibitory rate (%) as follows:

5      ulcer formation inhibitory rate (%) =

$$(1 - (UI \text{ in sample group}/UI \text{ in control group})) \times 100$$

## VOL. TAO: Acid Secretion Inhibition Test In Vivo

## 10 i) Meaning

Inhibitory effect on acid secretion in vivo is confirmed.

## ii) Method

Male Crj:Donryu rats (7-week-old) were fasted overnight but allowed free access to water. In each group, 8 to 10 of 15 these rats were used under urethane anesthesia (1.25 g/kg). The sample compound dissolved or suspended in an aqueous solution of 0.5% sodium carboxymethylcellulose or 0.05% Tween 80 was orally administered (100 mg/10 ml/kg). 30 minutes later, the abdomen of each was incised and the 20 pylorus was ligated. 30 minutes after the ligation, 30 mg/kg of histamine dissolved in physiological saline was subcutaneously administered and, 3 hours thereafter, the rat was sacrificed with carbon dioxide. Immediately thereafter, each 25 stomach was removed and the gastric contents were collected and each volume was determined. The total acid output was determined by titration of the gastric juice with 0.1N NaOH.

## iii) Judgment Standard

With respect to the gastric juice volume (VOL) and the 30 total acid output (TAO), the effects obtained when 100 mg/kg of the sample compound had been administered were expressed as their respective inhibitory rates (%) as follows:

each inhibitory rate (%) =

35       $(1 - (\text{value in sample group}/\text{value in control group})) \times 100$

## CAP: Acid Secretion Inhibition Test In Vitro

## i) Meaning

The acid secretion inhibitory activity in a cell level is 40 studied. It can also be used for studying the mechanism of the effect.

## ii) Method

ii-a) Preparation of isolated gastric fundus gland suspension

45      First, an isolated gastric fundic gland sample was prepared. Namely, a male Japanese White rabbit (2.5 to 3 kg) was anesthetized to death with Nembutal<sup>TM</sup> and then the abdomen was incised. Immediately thereafter, the stomach was removed and, after its pyloric and cardiac antrum were 50 severed, incised along its greater curvature into two sheets. The gastric contents adhering to the mucosal surface was washed out with ice-cooled PBS (-) and then carefully washed therein. The gastric wall was spread on a cork board with its mucosal surface facing up and the feed and mucus 55 thereon were completely removed with sterile gauze. The mucosa was separated therefrom by a spatula and then collected in ice-cooled PBS (-). After being washed twice with PBS (-), the mucosa was minced into 2-3 mm<sup>3</sup> pieces by scissors. These pieces were further washed twice with a 60 nutrient solution. The nutrient solution comprises 132.4 mM of NaCl, 5.4 mM of KCl, 5 mM of Na<sub>2</sub>HPO<sub>4</sub>·12H<sub>2</sub>O, 1 mM of NaH<sub>2</sub>PO<sub>4</sub>·2H<sub>2</sub>O, 1.2 mM of MgSO<sub>4</sub>, 1 mM of CaCl<sub>2</sub>, 25 mM of HEPES, 2 mg/ml of glucose, and 1 mg/ml of BSA. Into 70 ml of the nutrient solution containing 1 mg/ml of 65 collagenase, minced mucosal pieces were dispersed and intensely stirred in a conical flask with a stirrer at 37° C. for 40 to 60 minutes. During this period, 100% O<sub>2</sub> was sprayed

on the nutrient solution surface and the pH was appropriately measured such that it was immediately adjusted to pH 7.4, when the value was therebelow, with a base. The nutrient solution was added to the reaction solution so as to attain the total amount of about 200 ml. After being filtered through a mesh, the suspension was divisionally introduced into 50 ml centrifuge tubes and left for 15 minutes such that gastric fundic gland was deposited. The supernatant was repeatedly removed by an aspirator, dispersed in the nutrient solution, and then left such that the gastric fundic gland was washed three times. At this time, without using a pipette, the suspension was alternately introduced into two centrifuge tubes so as to effect dispersion. The number of cells was counted under microscope and adjusted to  $1.6 \times 10^6$  cells/ml.

ii-b)  $[^{14}\text{C}]$ -aminopyrine uptake test

Then,  $[^{14}\text{C}]$ -aminopyrine uptake test was performed. After an Eppendorf tube was weighed, 10  $\mu\text{l}$  (final concentration:  $10^{-5}\text{M}$ ) of histamine dissolved in the above-mentioned nutrient solution, 10  $\mu\text{l}$  (final concentration:  $10^{-5}\text{M}$ ) of the test compound dissolved in DMSO, and 10  $\mu\text{l}$  (final concentration: 0.05  $\mu\text{Ci}/\text{ml}$ ) of  $[^{14}\text{C}]$ -aminopyrine diluted with the nutrient solution were introduced therein and then 970  $\mu\text{l}$  of the isolated gastric fundic gland suspension prepared above was added thereto. Subsequently, this mixture was shaken at  $37^\circ\text{C}$ . for 40 minutes at 125 cycles/minute. After being centrifuged for 30 minutes, 200  $\mu\text{l}$  of its supernatant was collected into a mini-vial, while the rest was removed by an aspirator. The gland pellet was completely dried as the tube with its lid being opened was kept for one night in a drying oven at  $80^\circ\text{C}$ . and then the lid was closed and the weight was determined at room temperature. Then 100  $\mu\text{l}$  of 1N KOH was added thereto and the tube with its lid being closed was treated at  $60^\circ\text{C}$ . for 1 to 2 hours so as to dissolve the pellet. Then, the contents thereof were transferred to a mini-vial. Into the mini-vial containing the supernatant or gland pellet, 4 ml of Atom-lite™ was added and then the radioactivity was measured by a liquid scintillation counter. Here, after the radioactivity of the gland pellet was corrected by using a sample in which 20 mM of NaSCN was added so as to cancel the hydrogen ion concentration gradient, the integration ratio of aminopyrine specifically trapped by the gland pellet was calculated. This experiment was performed in duplicate.

ii-c) Calculation of the accumulation rate of aminopyrine

Here, its principle will be briefly explained. In the isolated gastric fundic gland, acid is accumulated in a space between its secretory tubule and intraglandular cavity. Aminopyrine is weak base ( $\text{pK}_a=5.0$ ) and nonionic in a neutral solution so as to freely pass through the cell membrane, whereas it is ionized in an acidic solution and thus cannot pass through the cell membrane due to its electric charge. Therefore, aminopyrine is accumulated in a closed acidic space within the isolated gastric fundic gland. In view of this characteristic, the accumulation rate ( $R$ ) of aminopyrine is calculated by the following equation:

$$R = ((\text{corrected radioactivity of precipitate}) / (\text{radioactivity of supernatant})) \times$$

$$(200 / (\text{mg dry weight of gland pellet}))$$

iii) Judgment Standard

The effect of the sample compound at the final concentration of  $10^{-5}\text{M}$  was expressed by acid secretion inhibitory rate (%) as follows:

$$\text{acid secretion inhibitory rate (\%)} =$$

$(1 - (R \text{ in sample group}/R \text{ in control group})) \times 100$

AHP: Antibacterial Activity Test Against *Helicobacter*  
 5 *pyroli*

i) Meaning

The minimum inhibitory concentration (MIC) against *Helicobacter pyroli* (microaerophilic gram-negative bacterium which is supposed to deeply involve in pathogenesis, 10 relapse, and recrudescence of ulcer, referred to as "HP" in the following) is measured so as to find out compounds which have antimicrobial activity against *Helicobacter pyroli*.

ii) Method

15 MICs were determined by the agar dilution method. The stock culture ( $\sim 80^\circ \text{C}$ .) of HP NCTC 11637 was thawed and cultured on tripticase soy agar supplemented with 5% sheep blood at  $37^\circ \text{C}$ . in an atmosphere of 5%  $\text{O}_2$ , 10%  $\text{CO}_2$ , and 85%  $\text{N}_2$ . Grown colonies were transferred to the same plate 20 and precultured for 3 days under the same condition. An appropriate amount of the colony grown on the plate by preculturing was suspended in Mueller Hinton broth till turbidness was recognizable by naked eyes, and diluted 100-fold in the same broth; this resulted in a bacterial 25 suspension for inoculation containing about  $10^5 \text{ cfu/ml}$  of the bacteria.

A 1.000  $\mu\text{g/ml}$  solution of the sample compound containing DMSO not more than 25% was seriesly diluted 2-fold in sterile purified water. 100  $\mu\text{l}$  volume from each dilution 30 was mixed thoroughly with 900  $\mu\text{l}$  of brucella agar supplemented with 5% horse blood and solidified in a 24 well micro plate, thereby yielding an MIC measurement plate.

10  $\mu\text{l}$  of the bacterial suspension for inoculation (about 35  $10^3 \text{ cfu}$ ) was inoculated on this plate and cultured for 7 days under the same condition as that of preculture. Thereafter, it was judged whether there had been bacteria growth or not.

iii) Judgment Standard

The minimum concentration of the sample compound when there were no visible colonies or, if any, 5 or less 40 colonies of HP was defined as MIC ( $\mu\text{g/ml}$ ).

PD: Gastric Mucosal Integrity Test

i) Meaning

There is a possibility that the anti-ulcer mechanism of the compounds which were effective in the experimental ulcer 45 model may be attributed to adaptive cytoprotection, which means exhibiting of apparent anti-ulcer effect due to increase in the amount of endogeneous prostaglandins in the gastric mucosa caused by necrotizing agents. In this case, since the sample compound has a necrotizing effect, it is 50 inappropriate as an anti-ulcer medicament.

Therefore, the gastric mucosal potential difference (PD), which reflects the integrity of the gastric mucosa, is measured so as to confirm that the sample compound has no 55 damaging effect on gastric mucosa, which is toxicity at gastric mucosal level.

ii) Method

Male Crj:SD rats (7 to 8-week-old) were fasted overnight, but allowed free access to water, and then, under urethane anesthesia (1.25 g/kg, i.p.), fixed to a cork board on its back. 60 The abdomen of each rat was incised, and a small incision was made in the forestomach. Then, the inside of the stomach was washed with physiological saline heated at  $37^\circ \text{C}$ . From the forestomach, along the greater curvature thereof, the stomach was incised without damaging blood 65 vessels. After the height of the cork board was adjusted on a jack, the stomach was mounted on ex vivo chamber. The area of the gastric mucosa exposed to the inside of this

chamber was  $2.5 \text{ cm}^2$ . The inside of the chamber was perfused with physiological saline warmed at  $37^\circ \text{ C}$ . by micro tube pump. By using an agar bridge containing 3M KCl, the potential difference between the chamber and the abdominal cavity was measured by a PD meter. Here, the rectal temperature was measured to control the body temperature during the experiment. After the PD was sufficiently stabilized, the perfuse was stopped and then 100 mg/10 ml/kg of the sample compound dissolved or suspended in an aqueous solution of 0.5% sodium carboxymethyl cellulose or 0.05% Tween 80 was administered into the chamber, while PD was recorded for 60 minutes. To a control, the vehicle was administered.

iii) Judgment Standard

The change in PD during 60 minutes after the administration of 100 mg/kg of the sample compound was collectively studied and, with reference to the positive control, classified into 5 levels as follows:

5: Same as the control with no recognizable damage at all.

4: Though a slight PD-decreasing tendency suggesting a slight possibility of mucosal damage is found, there is no problem.

3: Though a weak decrease in PD and a possibility of a weak mucosal damage is recognized, there is no substantial problem.

2: Medium degree of decrease in PD is found and a mucosal damage is recognized.

1: Heavy degree of decrease in PD is found and a remarkable mucosal damage is recognized.

AT: Single Dose Toxicity Pretest

i) Method

Male Slc:ICR mice (5-week-old) were used. Each group has 3 to 5 mice and each mouse was fasted, but allowed free access to water, for 4 to 5 hours from 9 a.m. in the test day. Then, 2,000 mg/10 ml/kg of the sample compound dissolved or suspended in an aqueous solution of 0.5% sodium carboxymethyl cellulose was orally administered thereto. To a control, only the vehicle was administered. The behavior and symptom were observed at each of 15 minutes, 30 minutes, 1 hour, 2 hours, and 3 hours after the administration and then daily till one week thereafter. The body weight was measured before and after the fasting as well as at the same time everyday. The dead animals were immediately subjected to autopsy and their organs were observed microscopically. Also, the living animals were sacrificed with ether or carbon dioxide one week after the administration and then their organs were observed microscopically.

ii) Judgment Standard

The toxicity at the single dose of 2,000 mg/kg of the sample compound was expressed as being classified into 5 levels.

5: Mortality rate is 0%: no toxicity is found at all both in behavior and organs.

4: Mortality rate is 0%: while no toxicity is found in organs, slight toxicity is observed in behavior and body weight increase.

3: While there is a dead animal (though not all the animals are dead), no toxicity is found in organs.

2: Regardless of whether there is a dead animal or not, toxicity is found in organs.

1: All the animals are dead.

MTT: Cell Damaging and Protecting Effect Test

i) Meaning

It is confirmed that there is no toxicity in cell level. Those having a toxicity in cell level are inappropriate as an anti-ulcer drug. Also, it can be confirmed that the effects of the sample compounds in other cell level tests do not result from their toxicity.

## ii) Method

A male Japanese White rabbit (2.5 to 3 kg) was anesthetized to death by Nembutal™ and, immediately thereafter, its stomach was removed. The greater curvature of the stomach was incised so as to remove the stomach contents therefrom. After the mucosal surface was washed with HBSS (Hanks' Balanced Salt Solution), the stomach in ice-cooled HBSS was transferred to a laboratory. Then, after the pyloric antrum was removed, the gastric corpus mucosa was separated by a spatula and then minced into 2 to 3 mm<sup>3</sup> pieces in BME (Basal Medium Eagle). Thereafter, these pieces were shaken at 120 to 130 cycles/minute for 15 minutes at 37° C. in BME 60 ml containing 280 U/ml of dispase and 30 to 50 U/ml of collagenase. Here, the concentration of collagenase was appropriately changed for each lot in view of the state of cells. The pieces were washed twice with EBSS (Earle's Balanced Salt Solution) containing 1 mM of EDTA and then shaken in MEM (Minimum Essential Medium) containing 1 mM of EDTA at 37° C. for 5 minutes. Subsequently, they were shaken in the dispase and collagenase having the same concentrations as those mentioned above for 15 minutes so as to remove the supernatant and then further shaken at 37° C. for 50 to 60 minutes at 120 to 130 cycles/minute. Then, after being washed twice with HBSS, Ham F12 containing 2% of Ultrocer G™ was used to attain the concentration of 1×10<sup>6</sup> cells/ml. Thus formed suspension was dispensed in each well of a 96-well plate by 200 µl. The plate was incubated in the atmosphere composed of 5% CO<sub>2</sub> and 95% air at 37° C. for three days so as to attain a confluent state and then subjected to MTT assay.

The sample compound was dissolved in DMSO so as to attain a concentration of 10<sup>-2</sup>M and then diluted with HBSS containing 2% of Ultrocer G™ so as to attain a final concentration of 10<sup>-4</sup>M. To each group, which 8 wells were used for, 10 µl of MTT reagent was added immediately after 100 µl of the medium in each well was exchanged for same volume of the resulting solution of the sample compound. After being incubated in an atmosphere composed of 5% CO<sub>2</sub> and 95% air at 37° C. for 4 hours, thus formed solution was centrifuged and then its supernatant was discarded. Subsequently, 100 µl of 100% ethanol was added to the residue so as to dissolve MTT formazan. Then, the absorbance (OD: 570 to 630) was measured by a microplate reader. This method utilizes a phenomenon in which MTT is changed to MTT formazan only by mitochondria of living cells so as to change color.

## iii) Judgment Standard

The cell damaging or cell protecting effect of the sample compound at the final concentration of 10<sup>-4</sup>M was expressed as cell damaging rate (%) as follows:

cell damaging rate (%) =

$$55 \quad (1 - (\text{absorbance in sample group}/\text{absorbance in control group})) \times 100$$

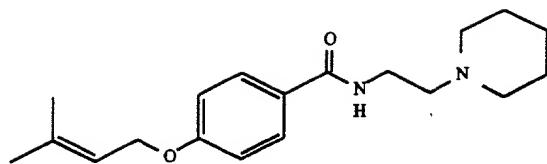
Accordingly, the smaller value is better in the cell damaging rate.

Based on the foregoing effect tests and safety tests, the effect and safety of the example compounds of the present invention were studied.

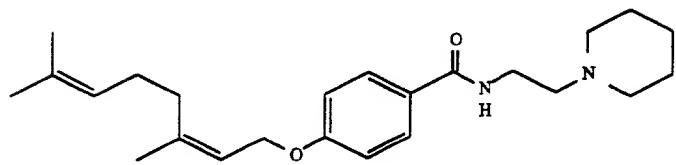
## Compound Group 1-1

This compound group has a structure expressed by formula 4 mentioned above, and wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms. As the alkylendiamine derivatives corresponding to this compound group 1-1, the following compounds were tested. The results of their effect tests and safety tests are shown in Table 1.

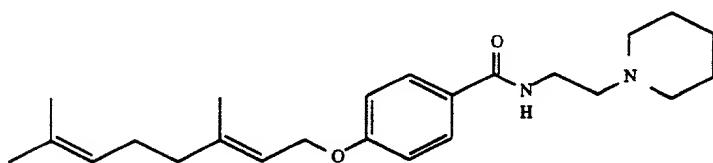
Example 1:



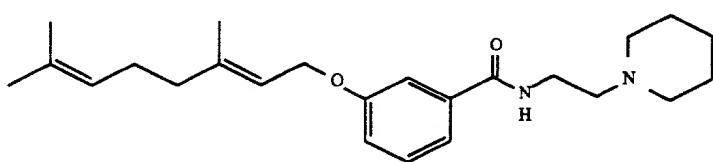
Example 2:



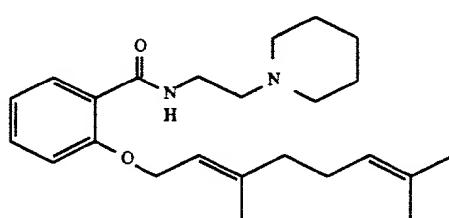
Example 3:



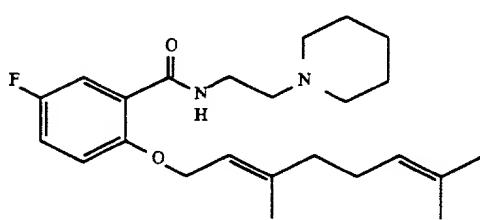
Example 4:



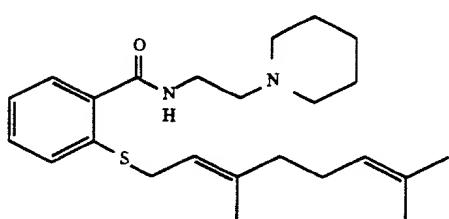
Example 5:



Example 6:



Example 7:

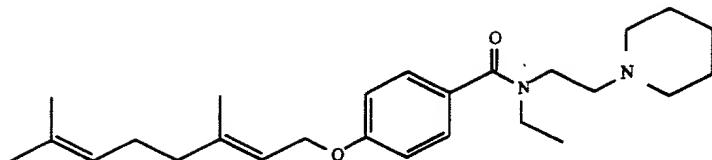


19

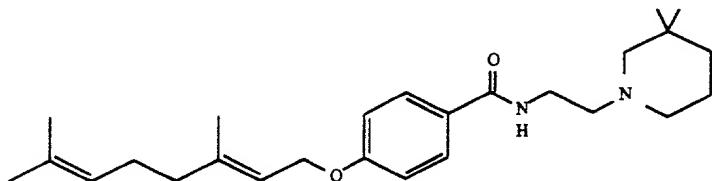
20

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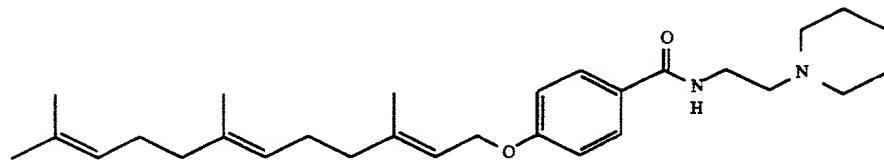
Example 8:



Example 9



Example 10



As clearly from Table 1, a compound of this compound group 1-1 has an excellent anti-ulcer effect and acid secretion inhibition effect.

Here, in this compound group 1-1, the bond position of the alkenyloxy group on the aromatic ring has a high degree of freedom. With respect to X, for example, as can be seen from Example 5 and Example 7, even when oxygen atom at X is substituted with sulfur atom, the effect has been maintained. Also, for example, from Example 5 and Example 6, it has been suggested that even when hydrogen atom at R<sub>1</sub> is substituted with fluorine atom, the effect has been maintained.

Further, from Example 3 and Example 8 to 9, it has been shown that even when hydrogen atom at R<sub>4</sub>, R<sub>5</sub>, or R<sub>6</sub> is substituted with a lower alkyl group, a sufficient effect can be obtained.

TABLE 1

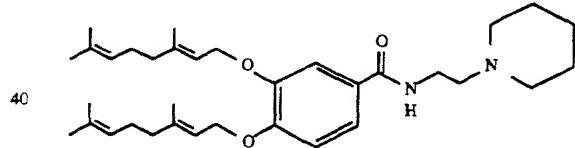
Example	Anti-ulcer Tests				Tests for Safety			
	No.	WIS	VOL	TAO	CAP	PD	AT	MTT
1	67						1	
2	79					3		
3	79	68		85	100	4		
4	84					3		
5	78						21	
6	80					3	16	
7	87							
8	67				100		41	
9	67							
10	47				98	5	4	

#### Compound Group 1-2

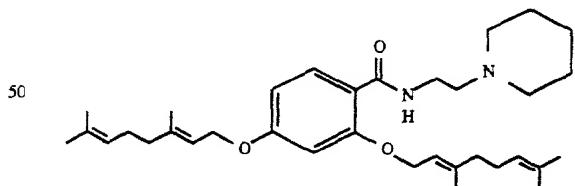
While in the compound group 1-1 mentioned above R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms, an alkylendiamine derivative in accordance with this compound group 1-2 has a basic structure wherein at least one of R<sub>1</sub> and R<sub>2</sub> in formula 4 mentioned above is an alkenyloxy group expressed by formula 5 mentioned above. As the alkylendiamine deriva-

30 tives corresponding to this compound group 1-2, the following compounds were tested. The results are shown in Table 2.

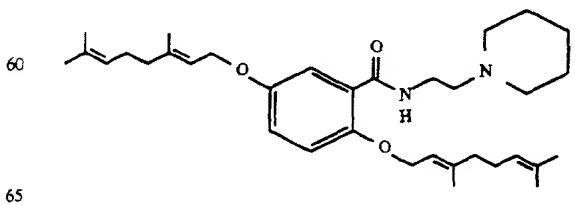
35 Example 11:



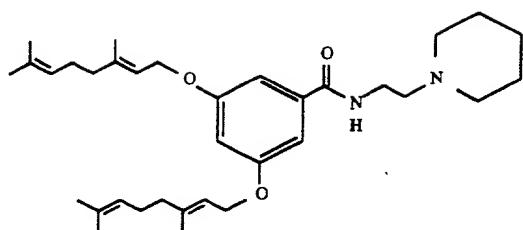
45 Example 12



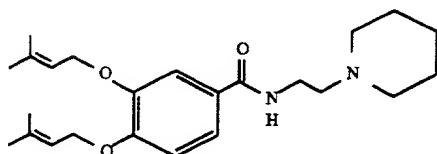
55 Example 13



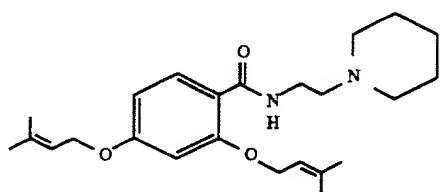
Example 14:



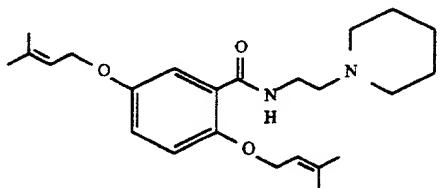
Example 15:



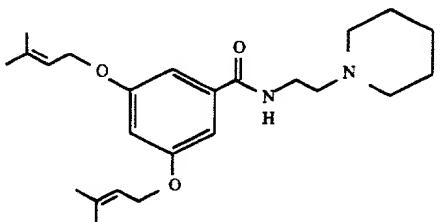
Example 16



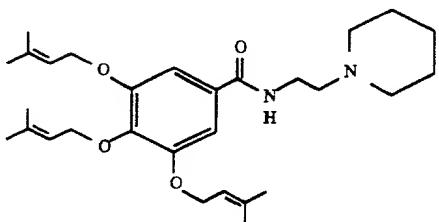
Example 17:



Example 18:



Example 19



As clearly from Table 2, even when  $R_1$  and/or  $R_2$  is an alkenyloxy group, a sufficient anti-ulcer effect and acid secretion inhibition effect can be obtained. Also, they are excellent in safety.

Here, in this compound group, the bond position of the alkenyloxy group can be selected with a high degree of

## 22

freedom, whereby it can bond to various bond position.

TABLE 2

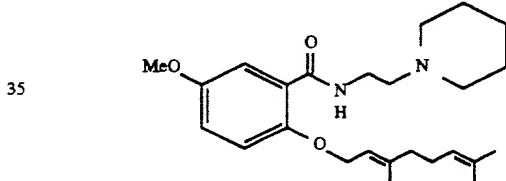
5	Example	Anti-ulcer Tests		Tests for Safety		
		No.	WIS	CAP	PD	AT
10	11	91			5	23
	12	75				38
	13	67	100		5	-5
	14	66			3	26
	15	89				17
	16	59				18
	17	70	100		3	-16
	18	40				33
	19	57			4	
15						

## Compound Group 1-3

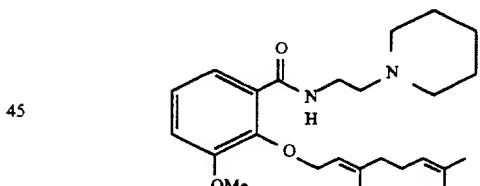
20 An alkylendiamine derivative of this compound group 1-3 has a basic structure expressed by formula 4 mentioned above, and wherein at least one of  $R_1$  and  $R_2$  is a lower alkoxy group.

25 As the alkylendiamine derivatives corresponding to this compound group 1-3, the following compounds were tested. The results are shown in Table 3.

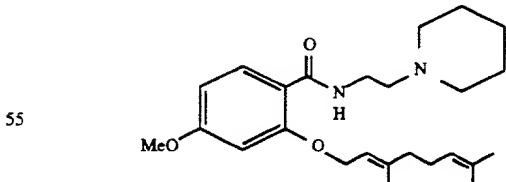
30 Example 20:



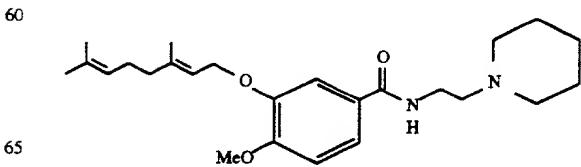
40 Example 21:



50 Example 22



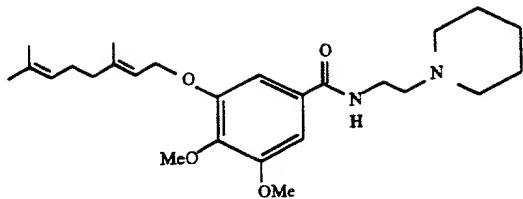
Example 23:



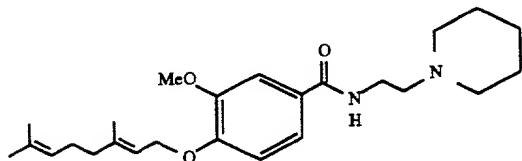
## 23

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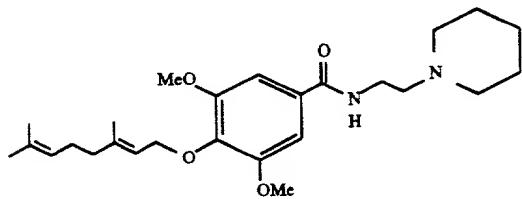
Example 24:



Example 25



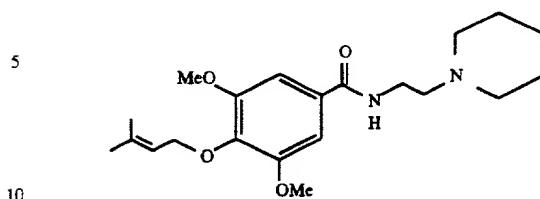
Example 26:



## 24

-continued

Example 27.



15 As clearly from Table 3, even when  $R_1$  and/or  $R_2$  is a lower alkoxy group, a sufficient anti-ulcer effect can be obtained. Especially, from Example 23 and 24, or from Example 25 and 26, it is suggested that when  $R_1$  and  $R_2$  are lower alkyl groups, more anti-ulcer effect and acid secretion inhibition effect can be obtained.

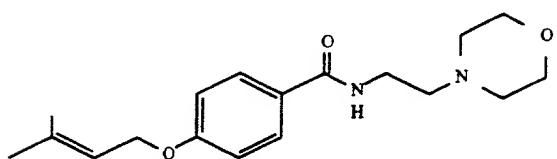
TABLE 3

20	Example	Anti-ulcer Test		Tests for Safety	
		No.	WIS	PD	AT
25	20		71		35
	21		68		12
	22		39		44
	23		56		43
	24		72		30
	25		44		48
	26		72		17
30	27		82	5	-11

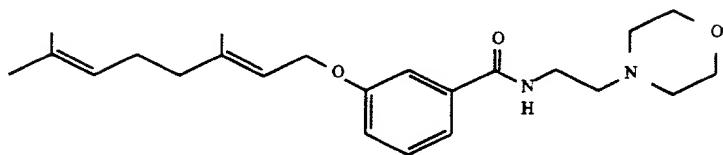
## Compound Group 2-1

An alkylenediamine derivative in accordance with this compound group 2-1 has a basic structure expressed by formula 6 mentioned above, and wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms. As the alkylenediamine derivatives corresponding to this compound group 2-1, the following compounds were tested.

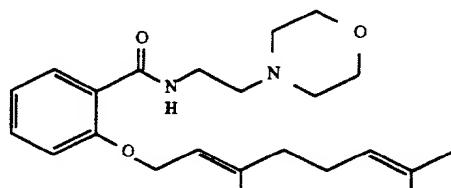
Example 28



Example 29



Example 30

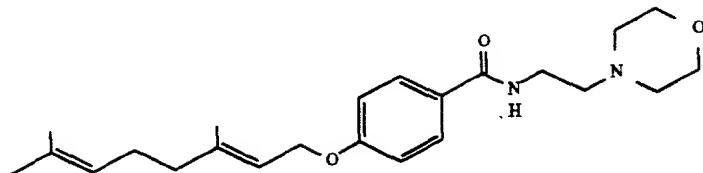


25

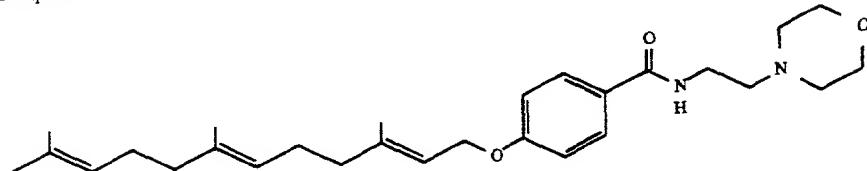
26

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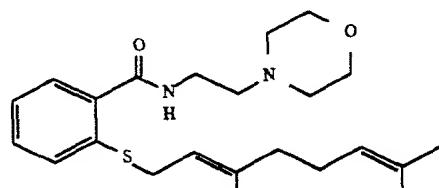
Example 31:



Example 32:



Example 33



Example 34:

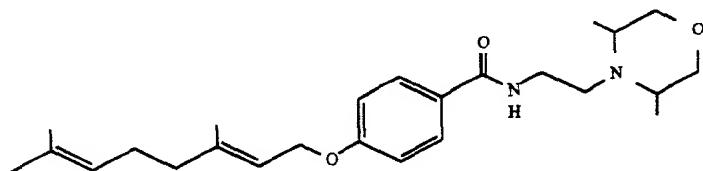


TABLE 4

Example	Anti-ulcer Tests			Tests for Safety		
	No.	WIS	CAP	PD	AT	MTT
28	64	88		5	3	-39
29	63	99			5	16
30	68					
31	54	99		3	5	15
32	55	99			5	58
33	49	100				5
34	38					14

As clearly from Table 4, even in this compound group 2-1 in which Y is  $-\text{O}-$ , a high anti-ulcer effect and acid secretion inhibition effect can be obtained.

Here, in this compound group, as Example 33 and Example 34, it is able to make oxygen atom at X into sulfur atom or to make R<sub>5</sub> and R<sub>6</sub> into lower alkyl groups.

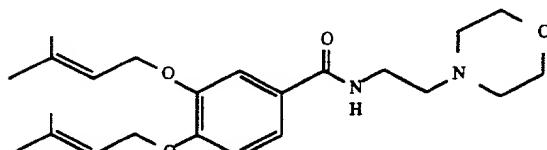
#### Compound Group 2-2

While in the compound group 2-1 mentioned above R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms, an alkylenediamine derivative in accordance with this compound group 2-2 has a basic structure wherein at least one of R<sub>1</sub> and R<sub>2</sub> in formula 6 mentioned above is an alkenyloxy group expressed by formula 5 mentioned above.

50

As the alkylenediamine derivatives corresponding to this compound group 2-2, the following compounds were tested. The results are shown in Table 5.

Example 35:

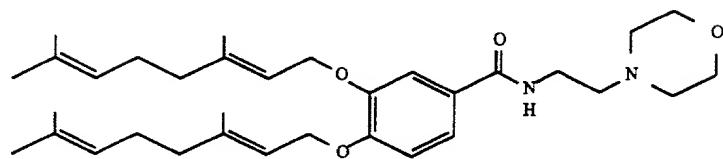


27

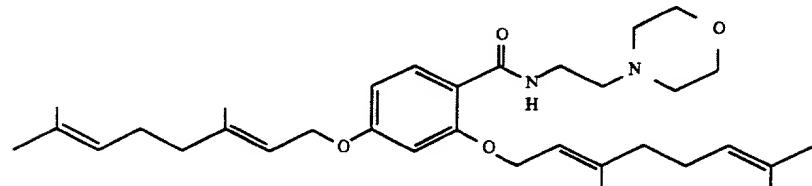
28

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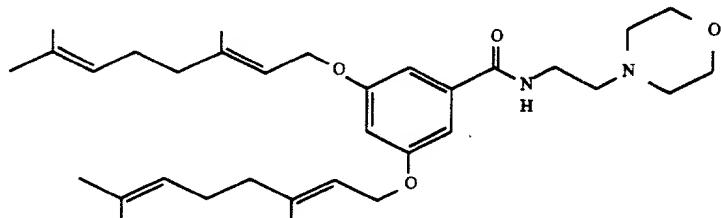
Example 36



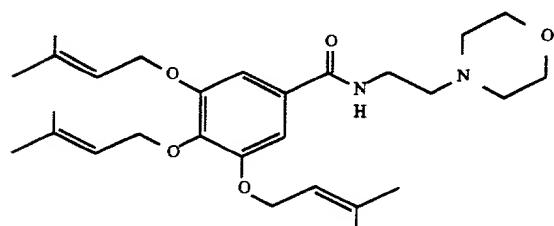
Example 37



Example 38



Example 39



25

TABLE 5

Example	Anti-ulcer Tests		Tests for Safety			
	No	WIS	CAP	PD	AT	MTT
35	48	100	5	4	-17	
36	39					
37	71					
38	55					-12
39	76			4		

As clearly from Table 5, even when  $R_1$  and/or  $R_2$  is an alkenyloxy group, an anti-ulcer effect and acid secretion inhibition effect can be obtained. Also, they are excellent in safety.

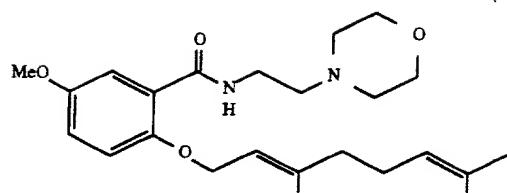
### Compound Group 3

50 An alkylenediamine derivative of this compound group 2-3 has a basic structure expressed by formula 6 mentioned above, and wherein at least one of  $R_1$  and  $R_2$  is a lower alkoxy group.

55 As the alkylenediamine derivatives corresponding to this compound group 2-3, the following compounds were tested.

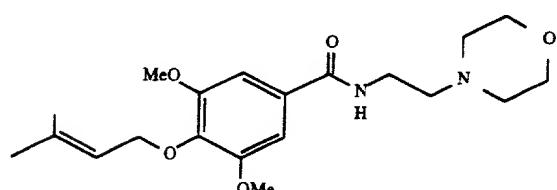
29

Example 40.

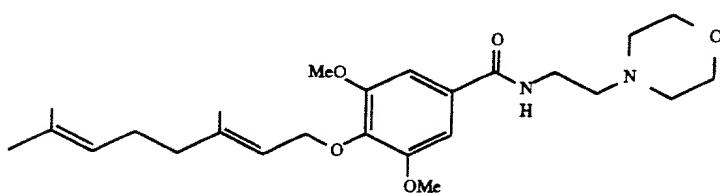


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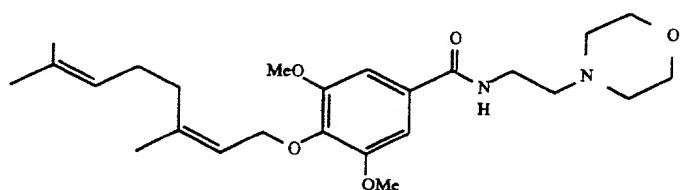
Example 41:



Example 42:



Example 43:



Example 44

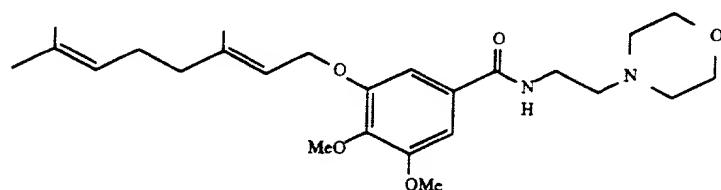


TABLE 6

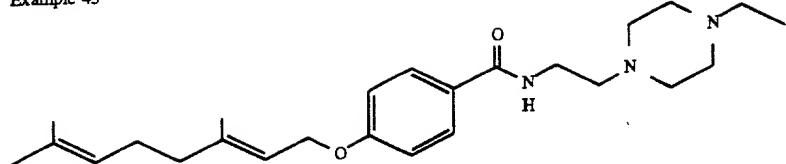
Example No	Anti-ulcer Tests		Tests for Safety		
	WIS	CAP	PD	AT	MTT
40	70				
41	39				
42	69	102		4	0
43	41		5	4	10
44	61	100		4	22

As clearly from Table 6, even when  $R_1$  and/or  $R_2$  is an alkoxy group, a sufficient anti-ulcer effect and acid secretion inhibition effect can be obtained.

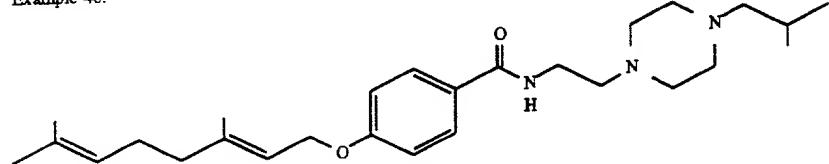
### 60 Compound Group 3

An alkylendiamine derivative of this compound group 3 has a basic structure expressed by formula 7 mentioned above, and wherein  $R_1$  and  $R_2$  are hydrogen atoms. As the alkylendiamine derivatives corresponding to this compound group 3, the following compounds were tested.

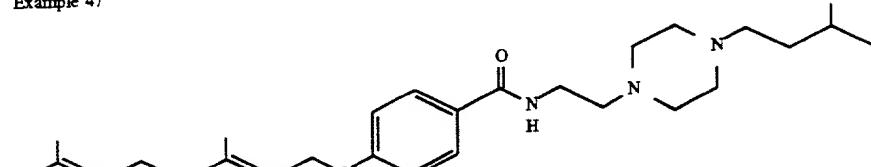
Example 45:



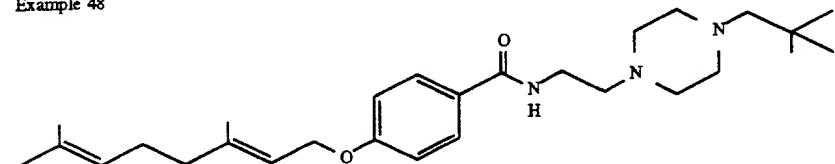
Example 46:



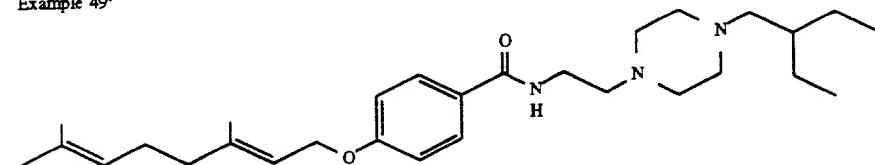
Example 47:



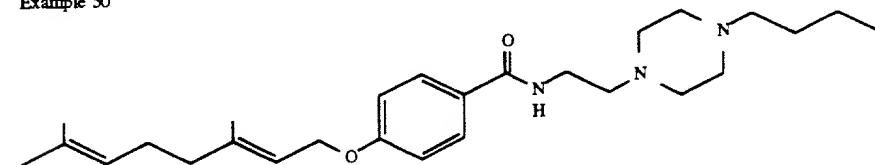
Example 48:



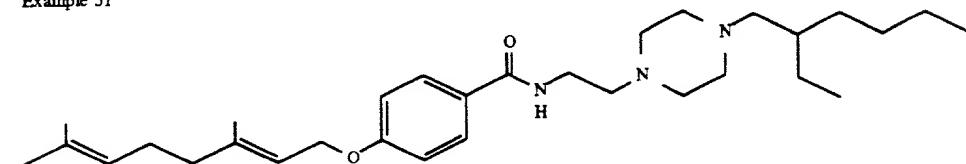
Example 49:



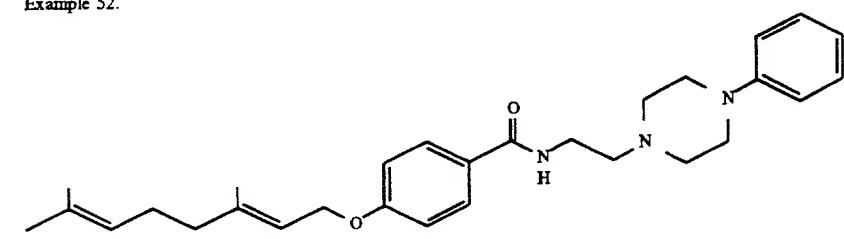
Example 50:



Example 51:

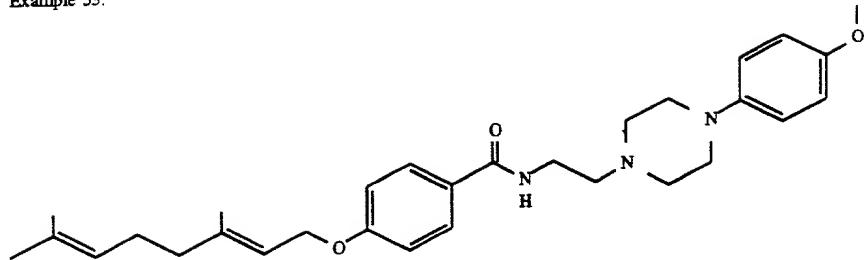


Example 52:

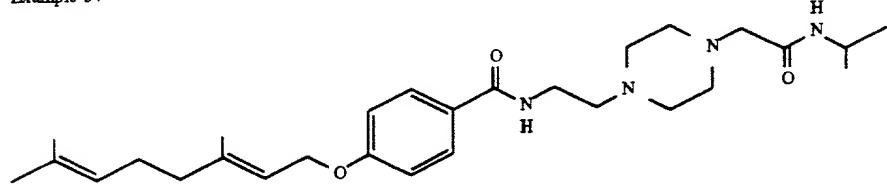


-continued

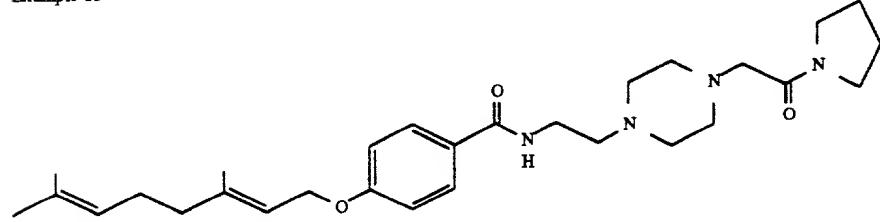
Example 53:



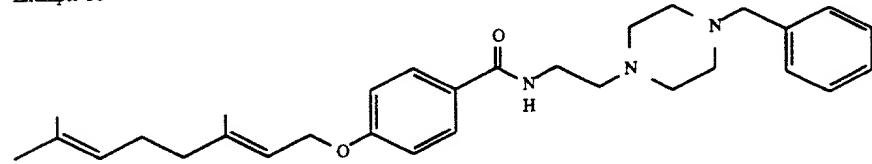
Example 54:



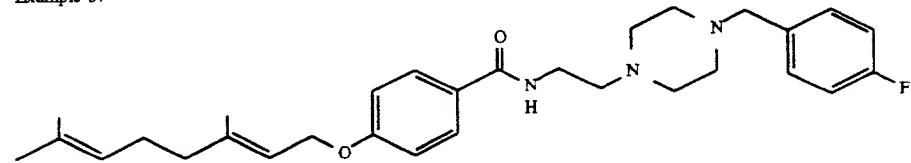
Example 55:



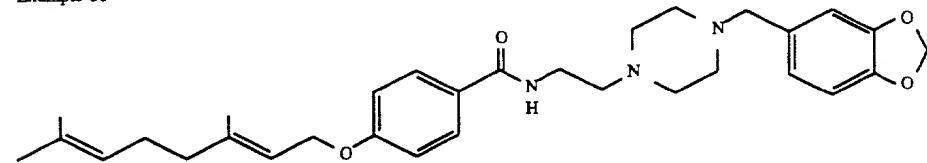
Example 56:



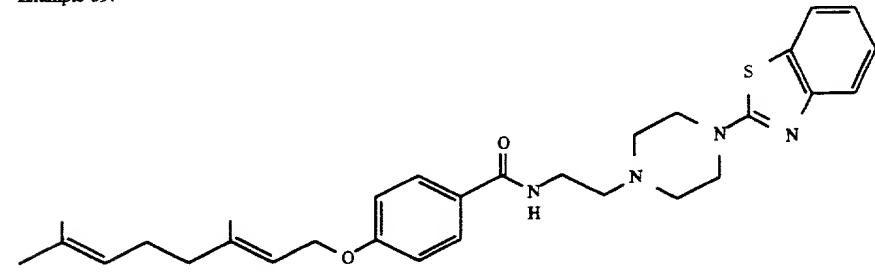
Example 57:



Example 58:

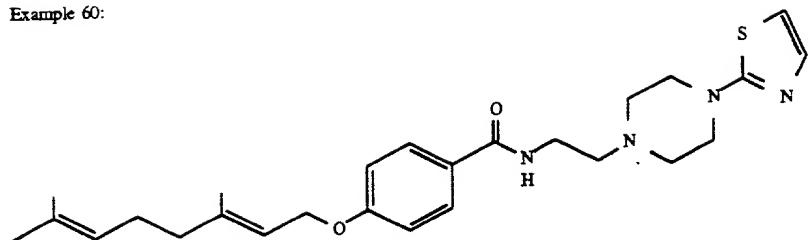


Example 59:

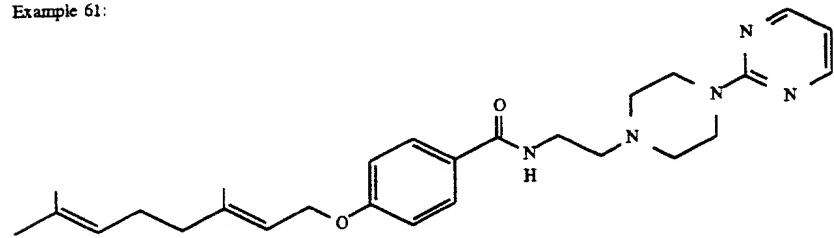


-continued

Example 60:



Example 61:



As clearly from results in Table 7, in this compound group 3, an anti-ulcer effect and acid secretion inhibition effect can be obtained. Further, as Example 59, there is a compound having an antibacterial activity against *Helicobacter pylori* together with.

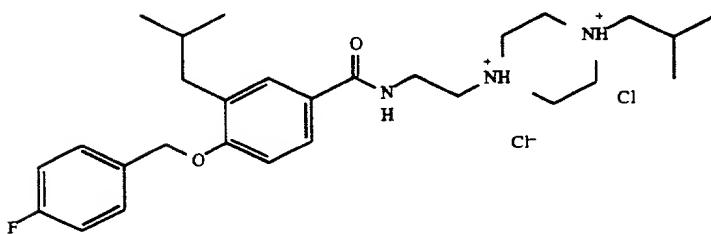
Here, in this compound group,  $R_7$  can be selected with a high degree of freedom, whereby  $R_7$  may be a lower alkyl group, an aryl group, a carbamoyl lower alkyl group, an aralkyl group, or an unsaturated heterocyclic group.

#### Compound Group 4

25

An alkylendiamine derivative in accordance with this compound group 4 has a basic structure expressed by formula 8 mentioned above. As the alkylendiamine derivative corresponding to the compound group 4, the following Example was tested.

Example 62.



45

TABLE 7

Example No.	Anti-ulcer Tests			Anti-HP Test	Test for Safety	
	WIS	VOL	TAO			
45	36			99	30	
46	78	33	34	100	68	
47				101.2		
48				100.1		
49				99.8		
50				95.9		
51				94.8		
52				99.1	11	
53				98.7	7	
54				100.0	27	
55				99.2		
56				99.4		
57				99.4		
58	48			100.0		
59	47			93.0	3.13>	7
60				100.1		7
61				100.1		3

TABLE 8

Example No.	Anti-ulcer Tests		Anti-HP Test	Test for Safety
	WIS	CAP		
62	77	102.5	3.13>	3

55 As can be seen from the foregoing Table 8, the compound of this compound group 4 has an anti-ulcer effect and acid secretion inhibition effect as well as an antibacterial activity against *Helicobacter pylori*.

56 In the following, the manufacturing method of Examples mentioned above will be explained.

60 At first, the synthetic methods of the material compounds used for synthesizing Examples of the present invention will be shown as Reference Examples 1 to 32.

#### Reference Example 1

##### 65 Synthesis of 4-geranyloxybenzoic acid

To a solution of methyl 4-hydroxybenzoate (7.61 g) in acetone(80 ml) were added geranyl bromide (10.9 g) and

potassium carbonate (13.8 g), and then the mixture was refluxed with heating for 6 hours. After the reaction, water (150 ml) was added to the reaction mixture, and the mixture was extracted with chloroform. The organic layer was dried over sodium sulfate anhydride and then concentrated under a vacuum. The residue was purified by silica gel column chromatography (hexane: ethyl acetate=9:1), thereby yielding 13.00 g of methyl 4-geranyloxybenzoate.

To a solution of methyl 4-geranyloxybenzoate(13.00 g) in methanol(50 ml) was added aqueous solution(10 ml) of potassium hydroxide (3.90 g). After being stirred overnight at room temperature, the mixture was refluxed with heating for 1 hour. After being acidified with concentrated hydrochloric acid, the reaction mixture was extracted with chloroform. The organic layer was dried over sodium sulfate anhydride and then the solvent was evaporated out under a vacuum. The resulting solid was recrystallized from hexane/ethyl acetate mixed solution, thereby yielding 9.77 g(71%) of the aimed compound.

#### Reference Example 2

##### Synthesis of 4-prenyloxybenzoic acid

In a manner identical to Reference Example 1, from methyl 4-hydroxy benzoate (7.61 g) and prenylbromide (7.45 g). 5.86 g (57%) of 4-prenyloxybenzoic acid was obtained.

#### Reference Example 3

##### Synthesis of 3-geranyloxybenzoic acid

In a manner identical to Reference Example 1, from methyl 3-hydroxy benzoate(7.61 g) and geranyl bromide (10.86 g). 8.45 g(62%) of 3-geranyloxybenzoic acid was obtained.

#### Reference Example 4

##### Synthesis of 2-geranyloxybenzoic acid

In a manner identical to Reference Example 1, from methyl 2-hydroxy benzoate(7.61 g) and geranyl bromide (10.86 g). 10.23 g(75%) of 2-geranyloxybenzoic acid was obtained.

#### Reference Example 5

##### Synthesis of 4-farnesyloxybenzoic acid

In a manner identical to Reference Example 1, from methyl 4-hydroxy benzoate(5.33 g) and farnesyl bromide (10.00 g). 7.58 g(63%) of 4-farnesyloxybenzoic acid was obtained.

#### Reference Example 6

##### Synthesis of 2-geranylthiobenzoic acid

In a manner identical to Reference Example 1, from methyl 4-mercaptop benzoate(8.36) and geranyl bromide (10.86 g). 10.97 g(76%) of 2-geranylthiobenzoic acid was obtained.

#### Reference Example 7

##### Synthesis of 2-geranyloxy-5-methoxybenzoic acid

To a solution of 2-hydroxy-5-methoxybenzoic acid (8.40 g) in ethanol (100 ml) was added sulfuric acid (5 ml) and then the mixture was refluxed with heating for 3 hours. After the reaction, the reaction mixture was concentrated and then water(100 ml) and sodium hydrogencarbonate were added thereto. The mixture was extracted with chloroform and the extract was purified by silica gel column chromatography (hexane: ethyl acetate), thereby yielding ethyl 2-hydroxy-5-methoxybenzoate.

In a manner identical to Reference Example 1, from the resulting compound (9.10 g) and geranyl bromide(10.86 g). 7.34 g(48%) of 2-geranyloxy-5-methoxybenzoic acid was obtained.

## Reference Example 8

## Synthesis of 3,4-diprenyloxybenzoic acid

In a manner identical to Reference Example 1. from ethyl 3,4-dihydroxy benzoate(9.10 g) and prenylbromide(14.90 g). 11.61 g(67%) of 3,4-diprenyloxybenzoic acid was obtained.

## Reference Example 9

## Synthesis of 3,4-digeranyloxybenzoic acid

10 In a manner identical to Reference Example 1. from ethyl 3,4-dihydroxy benzoate(9.10 g) and geranylchloride(21.70 g). 13.1 g(62%) of 3,4-digeranyloxybenzoic acid was obtained.

## Reference Example 10

## Synthesis of 2,4-digeranyloxybenzoic acid

15 In a manner identical to Reference Example 7. from 2,4-dihydroxybenzoic acid(9.10 g) and geranylchloride(21.70 g). 8.34 g(52%) of 2,4-digeranyloxybenzoic acid was obtained.

20

## Reference Example 11

## Synthesis of 4,5-dimethoxy-3-geranyloxybenzoic acid

20 In a manner identical to Reference Example 1. from methyl 4,5-dimethoxy-3-hydroxybenzoate(7.00 g) and geranylchloride(10.30 g). 5.62 g(51%) of 4,5-dimethoxy-3-geranyloxybenzoic acid was obtained.

## Reference Example 12

## Synthesis of methyl 3,5-dimethoxy-4-hydroxybenzoate

30 In a manner identical to Reference Example 7. from syringic acid (17.03 g) and methanol. 13.85 g(76%) of methyl 3,5-dimethoxy-4-hydroxybenzoate was obtained.

## Reference Example 13

## Synthesis of 3,5-dimethoxy-4-prenyloxybenzoic acid

35 In a manner identical to Reference Example 1. from methyl 3,5-dimethoxy-4-hydroxybenzoate(7.89 g) and prenylchloride(5.73 g). 5.40 g(55%) of 3,5-dimethoxy-4-prenyloxybenzoic acid was obtained.

40

## Reference Example 14

## Synthesis of 3,5-dimethoxy-4-geranyloxybenzoic acid

40 In a manner identical to Reference Example 1. from methyl 3,5-dimethoxy-4-hydroxybenzoate(5.44 g) and geranylchloride(8.04 g). 5.71 g(67%) of 3,5-dimethoxy-4-geranyloxybenzoic acid was obtained.

## Reference Example 15

## Synthesis of 4-neryoxybenzoic acid

50 To a solution of nerol(7.71 g) in dichloromethane(200 ml) were added N-chlorosuccinimide(10.01 g) and dimethylsulfide(6.56 ml) and then the mixture was stirred while being cooled with ice for 4 hours. After the reaction, the reaction mixture was washed with saturated brine and water successively, dried over sodium sulfate anhydride, and concentrated.

55

In a manner identical to Reference Example 1. from nerolchloride obtained and methyl 4-hydroxybenzoate(7.61 g). 7.47 g(54%) of 4-neryoxybenzoic acid was obtained.

## Reference Example 16

## 60 Synthesis of 3,5-dimethoxy-4-neryoxybenzoic acid

60 In a manner identical to Reference Example 15. from nerol(1.26 g) and methyl 3,5-dimethoxy-4-hydroxybenzoate (0.96 g). 0.19 g(9%) of 3,5-dimethoxy-4-neryoxybenzoic acid was obtained.

65

## Reference Example 17

## Synthesis of 3,4,5-triprenyloxybenzoic acid

In a manner identical to Reference Example 1, from ethyl 3,4,5-trihydroxy benzoate(4.95 g) and prenylbromide(14.90 g). 5.43 g(58%) of 3,4,5-triprenyloxybenzoic acid was obtained.

**Reference Example 18**

**Synthesis of 2-geranyloxy-4-methoxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 2-hydroxy-4-methoxybenzoate(9.1 g) and geranyl bromide(10.86 g). 7.73 g(51%) of 2-geranyloxy-4-methoxybenzoic acid was obtained.

**Reference Example 19**

**Synthesis of 4-geranyloxy-3-methoxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 4-hydroxy-3-methoxybenzoate(9.1 g) and geranyl bromide(10.86 g). 7.59 g(63%) of 4-geranyloxy-3-methoxybenzoic acid was obtained.

**Reference Example 20**

**Synthesis of 3-geranyloxy-4-methoxybenzoic acid**

In a manner identical to Reference Example 7, from 2-hydroxy-3-methoxybenzoic acid (16.80 g) and geranyl bromide (10.86 g). 11.54 g (64%) of 2-geranyloxy-3-methoxybenzoic acid was obtained.

**Reference Example 21**

**Synthesis of 3-geranyloxy-4-methoxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 3-hydroxy-4-methoxybenzoate(8.40 g) and geranyl bromide(10.36 g). 3.60 g(24%) of 3-geranyloxy-4-methoxybenzoic acid was obtained.

**Reference Example 22**

**Synthesis of 3,5-diprenyloxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 3,5-dihydroxy benzoate(8.40 g) and prenylbromide (14.90 g). 10.06 g(69%) of 3,5-diprenyloxybenzoic acid was obtained.

**Reference Example 23**

**Synthesis of 2,4-diprenyloxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 2,4-dihydroxy benzoate(8.40 g) and prenylbromide (14.90 g). 8.86 g(61%) of 2,4-diprenyloxybenzoic acid was obtained.

**Reference Example 24**

**Synthesis of 2,5-diprenyloxybenzoic acid**

In a manner identical to Reference Example 7, from methyl 2,5-dihydroxy benzoic acid (23.10 g) and prenylbromide (14.90 g). 9.74 g (84%) of 2,5-diprenyloxy benzoic acid was obtained.

**Reference Example 25**

**Synthesis of 3,5-digeranyloxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 3,5-dihydroxy benzoate(8.40 g) and geranyl bromide (21.72 g). 10.09 g(47%) of 3,5-digeranyloxybenzoic acid was obtained.

**Reference Example 26**

**Synthesis of 2,5-digeranyloxybenzoic acid**

In a manner identical to Reference Example 1, from methyl 2,5-dihydroxy benzoate(7.12 g) and geranyl bromide (21.72 g). 2.17 g(10%) of 2,5-digeranyloxybenzoic acid was obtained.

**Reference Example 27**

**Synthesis of 3-fluoro-6-geranyloxybenzoic acid**

40

In a manner identical to Reference Example 7, from 3-fluoro-6-hydroxybenzoic acid(10.00 g) and geranylbromide(10.86 g), 11.57 g(79%) of 3-fluoro-6-geranyloxybenzoic acid was obtained.

5

Reference Example 28

Synthesis of 4-(2-aminoethyl)-1-ethylpiperazine

To a solution of 1-piperazineethanol(2.28 g) in acetone(40 ml) were added bromoacetonitrile(2.40 g) and potassium carbonate(5.53 g) and then the mixture was stirred at room temperature for 4 hours. After the reaction, the reaction mixture was washed with saturated brine and water successively, dried over sodium sulfate anhydride, and concentrated under a vacuum. To the residue dissolved in methanol(60 ml) were added cobalt chloride(9.50 g) and sodium borohydride(7.60 g), and then the mixture was stirred at room temperature for 30 minutes. After the reaction mixture was concentrated, the resulting residue was dissolved in chloroform. After a filtration, the filtrate was concentrated, thereby yielding 1.17 g (41%) of 4-(2-aminoethyl)-1-ethylpiperazine.

Reference Example 29

Synthesis of 4-(2-aminoethyl)-1-isobutylpiperazine

1-piperazinecarboxaldehyde(33.21 g) and potassium carbonate(68.34 g) were dissolved in acetone(150 ml) and then isobutylbromide(47.43 g) was added thereto. After being refluxed with stirring for 24 hours, the reaction mixture was filtrated. The filtrate was concentrated under a vacuum and the resulting residue was dissolved in ethyl acetate. The solution was washed with water and saturated brine successively, dried over sodium sulfate anhydride, and concentrated under a vacuum, thereby yielding 36.85 g of residue. A solution of the residue (27.8 g) in methanol (160 ml), with 2N hydrochloric acid methanol solution (180 ml) added thereto, was stood at room temperature for 60 hours. The reaction mixture was concentrated under a vacuum and acetone was added to the resulting residue. The crystals deposited were collected by filtration, washed with acetone, and dried, thereby yielding 34.8 g of 1-isobutylpiperazine dihydrochloride.

To 1-isobutylpiperazine dihydrochloride(69.5 g) was added 10% aqueous solution of sodium hydrochloride(100 ml) and the mixture was extracted with ether. After being concentrated, the extract was distilled under a vacuum(bp 172°-174° C./5 mmHg), thereby yielding 43.7 g of 1-isobutylpiperazine.

By using 1-isobutylpiperazine (2.84 g) and bromoacetonitrile(2.40 g), as in the case of Reference Example 28, 1.19 g (15%) of 4-(2-aminoethyl)-1-isobutylpiperazine was obtained.

Reference Example 30

Synthesis of 1-(2-aminoethyl)-2,6-dimethylmorphorine

In a manner identical to Reference Example 28, from 2,6-dimethyl morphorine(3.46 g) and chloroacetonitrile (2.27 g), 2.97 g(63%) of 1-(2-aminoethyl)-2,6-dimethylmorphorine was obtained.

Reference Example 31

Synthesis of 1-[2-(ethylamino)ethyl]piperidine

To a solution of 1-(2-aminoethyl)piperidine(5.01 g) in dichloromethane (100 ml) were added triethylamine(11 ml) and acetic anhydride(4.4 ml) and then the mixture was stirred at room temperature for 40 minutes. The reaction solution was washed with saturated sodium hydrogencarbonate aqueous solution and saturated brine successively, dried over sodium sulfate anhydride, and concentrated under

a vacuum. The residue was dropped into a suspension of lithium aluminium hydride (3.46 g) in tetrahydrofuran(100 ml). After being refluxed with heating for 1 hour, the reaction mixture was filtrated. The filtrate was concentrated, thereby yielding 4.43 g(79%) of 1-[2-(ethylamino)ethyl]piperidine.

#### Reference Example 32

##### Synthesis of 1-(2-aminoethyl)-3,3-dimethylpiperidine

In a manner identical to Reference Example 28, from 3,3-dimethyl piperidine(3.40 g) and chloroacetonitrile(2.27 g). 2.32 g(50%) of 1-(2-aminoethyl)-3,3-dimethylpiperidine was obtained.

In the following, the synthesizing method of Examples 1 to 62 mentioned above which are compounds in accordance with the present invention will be shown.

#### Example 1

In a manner identical to Example 45, 4-prenyloxybenzoic acid(1.44 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(1.08 ml), thereby yielding 1.77 g(80%) of the aimed compound.

m.p. 86.2°-87.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.74(2H, d,J=8.8 Hz). 6.93(2H,d,J=8.8 Hz). 6.85(1H,bs). 5.49(1H,t, J=6.6 Hz). 4.55(2H,d,J=6.8 Hz). 3.51(2H,q,J=5.9 Hz). 2.54 (2H,t,J=6.1 Hz). 2.51-2.39(4H,m). 1.80 (3H,s). 1.75(3H,s). 1.61-1.58(4H,m). 1.50-1.42(2H,m).

#### Example 2

In a manner identical to Example 45, 4-neroyloxybenzoic acid(1.64 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.84 ml), thereby yielding 1.09 g(47%) of the aimed compound.

m.p. 59.8°-61.2 ° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H, d,J=8.8 Hz). 6.93(2H,d,J=8.8 Hz). 6.85(1H,bs). 5.50(1H,t, J=6.8 Hz). 5.12(1H,t,J=5.8 Hz). 4.54(2H,d,J=6.8 Hz). 3.51 (2H,q,J=5.8 Hz). 2.54(2H,t,J=5.8 Hz). 2.38-2.48(4H,m). 2.17-2.07(4H,m). 1.80(3H,s). 1.68(3H,s). 1.62-1.57(7H,m). 1.52-1.42(2H,m).

#### Example 3

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.70 g(88%) of the aimed compound.

m.p. 62.2-63.5° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H, dd,J=1.5 Hz,8.3 Hz). 6.92(2H,dd,J=2.0 Hz,8.8 Hz). 6.88 (1H,bs). 5.48 (1H,t,J=6.3 Hz). 5.13-5.06(1H,m). 4.57(2H, d,J=6.4 Hz). 3.51(2H,q,J=5.4 Hz). 2.55(2H,t,J=5.9 Hz). 2.51-2.39(4H,m). 2.18-2.02(4H,m). 1.74(3H,s). 1.67(3H,s). 1.60(3H,s). 1.50-1.42(2H,m).

#### Example 4

In a manner identical to Example 45, 3-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.75 g(91%) of the aimed compound.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.41-7.23(3H,m). 7.03(2H,dt, J=2.4 Hz,7.3 Hz). 6.99(1H,bs). 5.49(1H,t,J=6.4 Hz). 5.13-5.05(1H,m). 4.58(2H,d,J=6.4 Hz). 3.53(2H,q,J=5.4 Hz). 2.56(2H,t,J=6.1 Hz). 2.52-2.38(4H,m). 2.17-2.03(4H, m). 1.74(3H,s). 1.68(3H,s). 1.60(3H,s). 1.51-1.39(2H,m).

#### Example 5

In a manner identical to Example 45, 2-geranyloxybenzoic acid(1.37 g) was subjected to a con-

## 42

densation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.70 g(89%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.34(1H.bs). 8.21(1H.dd,J=2.0 Hz.7.8 Hz). 7.40(1H.dt,J=2.0 Hz.8.3 Hz). 7.05 (1H.t,J=7.8 Hz). 6.94(1H.d,J=8.3 Hz). 5.50(1H.t,J=6.4 Hz). 5.11–5.02(1H.m). 4.72(2H.d,J=6.4 Hz). 3.56(2H.q,J=6.4 Hz). 2.53(2H.t,J=6.4 Hz). 2.49–2.34(4H.m). 2.16–2.02 (4H.m). 1.75(3H.s). 1.66(3H.s). 1.60(3H.s). 1.49–1.39(2H.m).

### 10 Example 6

In a manner identical to Example 45, 5-fluoro-2-geranyloxybenzoic acid (1.46 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.06 g(53%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.40(1H.bs). 7.94–7.89(1H.m). 7.10–7.03(1H.m). 6.93–6.87(1H.m). 5.52–5.42(1H.m). 5.10–5.00(1H.m). 4.70(2H.d,J=6.4 Hz). 3.60–3.48(2H.m). 2.57–2.37 (6H.m). 2.15–2.05(4H.m). 1.74(3H.s). 1.66(3H.s). 1.60–1.44(9H.m).

### 20 Example 7

In a manner identical to Example 45, 2-geranylthiobenzoic acid(2.03 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (1.00 ml), thereby yielding 0.86 g(31%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.66(1H.d,J=8.8 Hz). 7.42–7.23(3H.m). 5.28(1H.t,J=7.8 Hz). 5.04(1H.t,J=6.8 Hz). 3.57–3.54(4H.m). 2.54(2H.t,J=6.4 Hz). 2.46–2.39(4H.m). 2.08–1.95(4H.m). 1.67(3H.s). 1.66(3H.s). 1.58(3H.s). 1.47–1.43(2H.m).

### Example 8

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.91 g) was subjected to a condensation reaction with 1-[2-(ethylamino)ethyl]piperidine (1.20 g), thereby yielding 2.13 g(74%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H.dd,J=1.5 Hz.8.3 Hz). 6.92(2H.dd,J=2.0 Hz.8.8 Hz). 5.48(1H.t,J=6.4 Hz). 5.13–5.06(1H.m). 4.57(2H.d,J=6.4 Hz). 3.75–3.20(4H.m). 2.72–2.20(6H.m). 2.18–2.02 (4H.m). 1.74(3H.s). 1.67(3H.s). 1.60(3H.s). 1.55(3H.s). 1.46(2H.s). 1.10–1.28(4H.m).

### 45 Example 9

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.92 g) was subjected to a condensation reaction with 1-(2-aminoethyl)-3,3-dimethylpiperidine (1.00 g), thereby yielding 1.63 g(56%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H.d,J=8.8 Hz). 6.92 (2H.d,J=8.8 Hz). 5.48(1H.t,J=6.6 Hz). 5.09(1H.t,J=6.6 Hz). 4.58(2H.d,J=6.3 Hz). 3.50(2H.q,J=5.4 Hz). 2.51(2H.t,J=5.9 Hz). 2.12–2.10 (6H.m). 1.74(3H.s). 1.68(3H.s). 1.62–1.60 (5H.m). 1.26(2H.t,J=6.8 Hz). 0.97(6H.s).

### Example 10

In a manner identical to Example 45, 4-farnesylbenzoic acid(1.71 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 2.23 g(99%) of the aimed compound.

m.p. 86.2°–87.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.74(2H. d,J=8.3 Hz). 6.93(2H.d,J=8.8 Hz). 6.88(1H.bs). 5.49(1H.t, J=6.6 Hz). 5.07–5.11(2H.m). 4.57(2H.d,J=6.8 Hz). 3.51(2H. q,J=5.4 Hz). 2.55(2H.t,J=6.1 Hz). 2.51–2.39(4H.m). 2.15–2.03(6H.m). 1.75(3H.s). 1.68(3H.s). 1.60–1.57(12H. m).

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#### Example 11

In a manner identical to Example 45, 3.4-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 2.17 g(81%) of the aimed compound.

m.p. 99.5°–100.8° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.43 (1H,d,J=2.0 Hz), 7.28–7.23(1H.m), 6.87(1H,d,J=8.3 Hz), 5.56–5.45 (2H.m), 5.12–5.03(2H.m), 4.66(4H,d,J=6.4 Hz), 3.54–3.46(2H.m), 2.56–2.48(2H.m), 2.47–2.34(4H.m), 2.15–2.00(8H.m), 1.74(3H.s), 1.72(3H.s), 1.66(6H.s), 1.59 (6H.s), 1.51–1.39(2H.m).

#### Example 12

In a manner identical to Example 45, 2.4-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 2.10 g(79%) of the aimed compound.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 8.20(1H.bs), 8.15(1H,d,J=8.8 Hz), 6.58(1H,dd,J=2.0 Hz,6.8 Hz), 6.49(1H,d,J=2.0 Hz), 5.52–5.46(2H.m), 5.09–5.07(2H.m), 4.67(2H,d,J=6.4 Hz), 4.56(2H,d,J=6.4 Hz), 3.54(2H,d,J=4.9 Hz), 2.59–2.45(2H.m), 2.42(4H.bs), 2.15–2.05(8H.m), 1.74 (6H.s), 1.68–1.67 (6H.m), 1.60–1.59(2H.m).

#### Example 13

In a manner identical to Example 45, 2.5-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 2.06 g(77%) of the aimed compound.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 8.43(1H.bs), 7.79(1H,d,J=3.4 Hz), 6.99(1H,dd,J=3.4 Hz,8.8 Hz), 6.90(1H,d,J=8.8 Hz), 5.53–5.42(2H.m), 5.11–5.02(2H.m), 4.63(2H,d,J=6.4 Hz), 4.52(2H,d,J=6.4 Hz), 3.52(2H,q,J=6.4 Hz), 2.55(2H,t,J=6.4 Hz), 2.50–2.37(4H.m), 2.17–2.02 (8H.m), 1.72(6H.s), 1.67 (6H.s), 1.60(6H.s), 1.51–1.39(2H.m).

#### Example 14

In a manner identical to Example 45, 3.5-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 2.24 g(84%) of the aimed compound.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 6.94(2H,d,J=2.4 Hz), 6.61 (1H,t,J=2.4 Hz), 5.49(2H,t,J=5.4 Hz), 5.12–5.04 (2H.m), 4.51(4H,d,J=6.8 Hz), 3.52(2H,q,J=5.9 Hz), 2.56(2H,t,J=5.8 Hz), 2.51–2.37 (4H.m), 2.17–2.04(8H.m), 1.73(6H.s), 1.68 (6H.s), 1.60(6H.s), 1.50–1.41(2H.m).

#### Example 15

In a manner identical to Example 45, 3.4-diprenyloxybenzoic acid(1.45 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.80 g(90%) of the aimed compound.

m.p. 101.5°–102.5° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.43 (1H,d,J=2.0 Hz), 6.85(1H,d,J=8.3 Hz), 5.55–5.46(2H.m), 4.62(4H,d,J=4.4 Hz), 3.56–3.48(2H.m), 2.58–2.52(2H.m), 2.51–2.40(4H.m), 1.77(6H.s), 1.74 (3H.s), 1.73(3H.s), 1.64–1.51(4H.m), 1.51–1.43(2H.m).

#### Example 16

In a manner identical to Example 45, 2.4-diprenyloxybenzoic acid(1.45 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.88 g(94%) of the aimed compound.

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<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.19–8.15(2H.m), 6.59(1H.d, J=2.4 Hz), 6.49(1H.d, J=2.2 Hz), 5.52–5.48 (2H.m), 4.63 (2H.d, J=5.9 Hz), 4.54(2H.d, J=6.3 Hz), 3.56–3.53(2H.m), 2.52(2H.t, J=6.4 Hz), 2.42(4H.s), 1.80(6H.s), 1.75(6H.s), 1.58–1.57(4H.m), 1.49–1.40(2H.m).

### Example 17

In a manner identical to Example 45, 2.5-diprenyloxybenzoic acid(1.45 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(0.70 ml), thereby yielding 1.68 g(84%) of the aimed compound.

m.p. 46.0°–47.8° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.43(1H. bs), 7.79(1H.d, J=3.4 Hz), 6.99(1H.dd, J=3.4 Hz, 8.8 Hz), 6.90(1H.d, J=8.8 Hz), 5.51–4.95(2H.m), 4.63(2H.d, J=6.4 Hz), 4.52(2H.d, J=6.4 Hz), 3.52(2H.q, J=6.4 Hz), 2.55(2H.t, J=6.4 Hz), 2.50–2.37(4H.m), 1.80(6H.s), 1.74(6H.s), 1.51–1.39(2H.m).

### Example 18

<sup>20</sup> In a manner identical to Example 45, 3.5-diprenyloxybenzoic acid(2.03 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(1.00 ml), thereby yielding 2.22 g(79%) of the aimed compound.

<sup>25</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 6.94(2H.d, J=2.4 Hz), 6.61 (1H.t, J=2.4 Hz), 5.49(2H.t, J=5.4 Hz), 4.51(4H.d, J=6.8 Hz), 3.52(2H.q, J=5.9 Hz), 2.56(2H.t, J=5.8 Hz), 2.51–2.37(4H.m), 1.80(6H.s), 1.74(6H.s), 1.64–1.55(4H.m), 1.50–1.41 (2H.m).

### Example 19

<sup>30</sup> In a manner identical to Example 45, 3.4.5-triprenyloxybenzoic acid(13.11 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine(5.42 ml), thereby yielding 11.98 g(71%) of the aimed compound.

<sup>35</sup> m.p. 75.0–79.5° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.02(2H.s), 6.84(1H.s), 5.56–5.42(3H.m), 4.62–4.50(6H.m), 3.53–3.40 (2H.m), 2.57–2.47(2H.m), 2.46–2.34(4H.m), 1.78–1.52(22H.m), 1.50–1.37(2H.m).

### Example 20

<sup>40</sup> In a manner identical to Example 45, 2-geranyloxy-5-methoxybenzoic acid(1.52 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.70 g(82%) of the aimed compound.

<sup>45</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.45(1H.bs), 7.76(1H.d, J=3.0 Hz), 7.06–6.82(2H.m), 5.77–5.50(1H.m), 5.10–4.94(1H.m), 4.67(2H.d, J=6.8 Hz), 3.81(3H.s), 3.61–3.46(2H.m), 2.06–2.30(6H.m), 2.13–2.00(4H.m), 1.72(3H.s), 1.67(3H.s), 1.60(3H.s), 1.49–1.35(2H.m).

### Example 21

<sup>50</sup> In a manner identical to Example 45, 2-geranyloxy-3-methoxybenzoic acid(1.52 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.49 g(72%) of the aimed compound.

<sup>55</sup> <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.38(1H.bs), 7.70(1H.dd, J=2.0 Hz, 7.8 Hz), 7.12(1H.dt, J=2.0 Hz, 7.8 Hz), 7.00 (1H.d, J=8.3 Hz), 5.53(1H.t, J=7.3 Hz), 5.07–5.02(1H.m), 4.64(2H.d, J=7.3 Hz), 3.89 (3H.s), 3.56(2H.q, J=6.3 Hz), 2.53(2H.t, J=6.3 Hz), 2.49–2.33(4H.m), 2.12–1.97 (4H.m), 1.67(3H.s), 1.62(3H.s), 1.59(3H.s), 1.48–1.39(2H.m).

### Example 22

<sup>60</sup> In a manner identical to Example 45, 2-geranyloxy-4-methoxybenzoic acid(1.52 g) was subjected to a condensa-

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tion reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.39 g(67%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.22(1H,bs), 8.17(1H,d,J=8.8 Hz), 6.57(1H,dd,J=2.0 Hz,8.8 Hz), 6.47(1H,d,J=2.0 Hz), 5.56–5.47(1H,m), 5.10–5.03(1H,m), 4.69(2H,d,J=6.4 Hz), 3.83(3H,s), 3.55 (2H,q,J=6.4 Hz), 2.52(2H,t,J=6.4 Hz), 2.48–2.35(4H,m), 2.17–2.04(4H,m), 1.76(3H,s), 1.66(3H,s), 1.60(3H,s), 1.50–1.36(2H,m).

### Example 23

In a manner identical to Example 45, 3-geranyloxy-4-methoxybenzoic acid(1.54 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.56 g(75%) of the aimed compound.

m.p. 101.0°–102.5° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.45 (1H,bs), 7.28(1H,d,J=8.3 Hz), 6.87(1H,d,J=8.3 Hz), 5.54 (1H,t,J=6.4 Hz), 5.09(1H,t,J=6.8 Hz), 4.66(2H,d,J=6.8 Hz), 3.90(3H,s), 3.51(2H,q,J=5.4 Hz), 2.55(2H,t,J=5.4 Hz), 2.51–2.36(4H,m), 2.16–2.04(4H,m), 1.75(3H,s), 1.66(3H,s), 1.60(3H,s), 1.52–1.41(2H,m).

### Example 24

In a manner identical to Example 45, 4,5-dimethoxy-3-geranyloxybenzoic acid(1.34 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.62 ml), thereby yielding 1.60 g(90%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.25–7.07(2H,m), 5.52(1H,t, J=5.4 Hz), 5.08(1H,t,J=5.4 Hz), 4.64(2H,d,J=6.8 Hz), 3.90 (3H,s), 3.88(3H,s), 3.55–3.51(2H,m), 2.58(2H,t,J=5.9 Hz), 2.55–2.38 (4H,m), 2.13–2.05(4H,m), 1.74(3H,s), 1.67(3H, s), 1.60(3H,s), 1.65–1.42(6H,m).

### Example 25

In a manner identical to Example 45, 4-geranyloxy-3-methoxybenzoic acid(1.52 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.70 ml), thereby yielding 1.71 g(83%) of the aimed compound.

m.p. 82.2°–82.8° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.44(1H, d,J=2.0 Hz), 7.25(1H,dd,J=2.0 Hz,8.3 Hz), 6.86(1H,d,J=8.3 Hz), 6.91 (1H,bs), 5.50(1H,t,J=6.8 Hz), 5.08(1H,t,J=6.4 Hz), 4.66(2H,d,J=6.4 Hz), 3.91(3H,s), 3.52 (2H,q,J=6.4 Hz), 2.55(2H,t,J=6.4 Hz), 2.50–2.37(4H,m), 2.16–1.96(4H,m), 1.73(3H,s), 1.67(3H,s), 1.59(3H,s), 1.51–1.39(2H,m).

### Example 26

In a manner identical to Example 45, 3,5-dimethoxy-4-geranyloxybenzoic acid(1.80 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (0.69 g), thereby yielding 0.70 g(29%) of the aimed compound.

m.p. 70.0°–72.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.03(2H, s), 6.95(1H,s), 5.60–5.52(1H,m), 5.12–5.05(1H,m), 4.58 (2H,d,J=7.3 Hz), 3.90(6H,s), 3.57–3.50(2H,m), 2.65–2.55 (2H,m), 2.53–2.40(4H,m), 2.09–2.03(4H,m), 1.88–1.58 (13H,m), 1.52–1.42(2H,m).

### Example 27

In a manner identical to Example 45, 3,5-dimethoxy-4-prenyloxybenzoic acid(1.86 g) was subjected to a condensation reaction with 1-(2-aminoethyl)piperidine (1.08 ml), thereby yielding 1.56 g(59%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.04(2H,d,J=3.9 Hz), 5.55 (1H,t,J=5.4 Hz), 4.54(2H,t,J=5.4 Hz), 3.90(6H,s), 3.57–3.45 (2H,m), 3.63–3.40(6H,m), 1.74(3H,s), 1.67(3H,s), 1.60–1.48(3H,m).

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## Example 28

In a manner identical to Example 45, 4-prenyloxybenzoic acid(1.44 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine (1.00 ml), thereby yielding 1.77 g(80%) of the aimed compound.

m.p. 114.8°–115.5° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73 (2H,d,J=8.8 Hz), 6.94(2H,d,J=8.8 Hz), 6.66(1H,bs), 5.49 (1H,t,J=5.4 Hz), 4.56(2H,d,J=6.8 Hz), 3.73(4H,t,J=4.4 Hz), 10 3.54(2H,q,J=5.8 Hz), 2.59(2H,t,J=5.9 Hz), 2.50 (4H,t,J=4.4 Hz), 1.81(3H,s), 1.76(3H,s).

## Example 29

In a manner identical to Example 45, 15 3-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine (0.70 ml), thereby yielding 1.73 g(90%) of the aimed compound.

m.p. 54.8°–57.2° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.41–7.25 (3H,m), 7.05(2H,dt,J=2.4 Hz,8.6 Hz), 6.74(1H,bs), 5.49(1H, t,J=6.3 Hz), 5.12–5.06(1H,m), 4.58(2H,d,J=6.3 Hz), 3.73 (4H,t,J=4.9 Hz), 3.55(2H,q,J=5.9 Hz), 2.60(2H,t,J=5.9 Hz), 2.55–2.41(4H,m), 2.16–2.04(4H,m), 1.75(3H,s), 1.68 (3H, s), 1.61(3H,s).

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## Example 30

In a manner identical to Example 45, 2-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine (0.70 ml), thereby yielding 1.71 g(89%) of the aimed compound.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 8.33(1H,bs), 8.20(1H,dd,J=1.5 Hz,7.8 Hz), 7.41(1H,dt,J=2.0 Hz,7.3 Hz), 7.06 (1H,t,J=7.3 Hz), 6.96(1H,d,J=8.3 Hz), 5.49(1H,t,J=6.4 Hz), 5.09–5.01(1H,m), 4.73(2H,d,J=6.4 Hz), 3.72(4H,t,J=4.6 Hz), 3.58(2H,q,J=6.4 Hz), 2.57(2H,t,J=6.4 Hz), 2.53–2.44 (4H,m), 2.18–2.01(4H,m), 1.76(3H,s), 1.67(3H,s), 1.60(3H, s).

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## Example 31

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine (0.70 ml), thereby yielding 1.46 g(76%) of the aimed compound.

m.p. 85.2°–87.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H, d,J=8.6 Hz), 6.92(2H,d,J=8.6 Hz), 6.76(1H,bs), 5.57–5.43 (1H,m), 5.15–5.06(1H,m), 4.58(2H,d,J=6.3 Hz), 3.73(4H,t, J=4.7 Hz), 3.55(2H,q,J=5.9 Hz), 2.62 (2H,t,J=6.3 Hz), 2.59–2.48(4H,m), 2.22–2.04(4H,m), 1.74(3H,s), 1.68(3H,s), 50 1.60 (3H,s).

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## Example 32

In a manner identical to Example 45, 4-farnesylbenzoic acid(1.71 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine (0.70 ml), thereby yielding 2.18 g(96%) of the aimed compound.

m.p. 68.6°–71.2° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H, d,J=8.8 Hz), 6.94(2H,d,J=8.8 Hz), 6.66(1H,bs), 5.48(1H,t, t,J=5.4 Hz), 5.06–5.16(2H,m), 4.58(2H,d,J=5.4 Hz), 3.73(4H, t,J=4.4 Hz), 3.54(2H,q,J=5.4 Hz), 2.60 (2H,t,J=5.8 Hz), 2.45–2.55(4H,m), 2.17–1.92(6H,m), 1.75(3H,s), 1.68(3H,s), 1.60 (6H,s).

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## Example 33

In a manner identical to Example 45, 2-geranylthiobenzoic acid(2.03 g) was subjected to a con-

densation reaction with 1-(2-aminoethyl)morphorine (1.00 ml), thereby yielding 1.43 g(51%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.67(1H,d,J=7.4 Hz), 7.41–7.39(1H,m), 7.35–7.23(2H,m), 5.27(1H,t,J=7.8 Hz), 5.04(1H,t,J=6.4 Hz), 4.73(2H,d,J=6.4 Hz), 3.70(4H,t,J=4.9 Hz), 3.60–3.54(4H,m), 2.60 (2H,t,J=6.4 Hz), 2.50(4H,t,J=5.4 Hz), 2.07–1.97(4H,m), 1.67(3H,s), 1.58(3H,s), 1.54 (3H, s).

#### Example 34

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.92 g) was subjected to a condensation reaction with 1-(2-aminoethyl)-2,6-dimethyl morphorine(1.00 g), thereby yielding 1.20 g(41%) of the aimed compound.

m.p. 74.6°–75.8° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.72(2H, d,J=8.8 Hz), 6.90(2H,d,J=8.8 Hz), 6.72–6.92(1H,m), 5.38–5.54 (1H,m), 5.00–5.16(1H,m), 4.56(2H,d,J=6.4 Hz), 3.63–3.81(2H,m), 3.57(2H,q,J=5.9 Hz), 2.81(2H,d,J=10.7 Hz), 2.62(2H,t,J=5.9 Hz), 1.95–2.25(4H,m), 1.84(2H,t,J=10.7 Hz), 1.74 (3H,s), 1.68(3H,s), 1.60(3H,s), 1.17(6H,d,J=6.4 Hz).

#### Example 35

In a manner identical to Example 45, 3,4-diprenyloxybenzoic acid(1.45 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine(0.67 ml), thereby yielding 1.76 g(88%) of the aimed compound.

m.p. 119.0°–120.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.43 (1H,d,J=2.0 Hz), 6.85(1H,d,J=8.3 Hz), 5.61–5.46(2H,m), 4.63(4H,d,J=6.8 Hz), 3.72(4H,t,J=4.3 Hz), 3.54(2H,q,J=5.9 Hz), 2.60(2H,t,J=5.9 Hz), 2.50(4H,d,J=4.4 Hz), 1.77(6H,s), 1.74(3H,s), 1.73(3H,s).

#### Example 36

In a manner identical to Example 45, 3,4-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine(0.70 ml), thereby yielding 2.29 g(85%) of the aimed compound.

m.p. 113.5°–114.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.43 (1H,d,J=2.0 Hz), 7.28–7.23(1H,m), 6.87(1H,d,J=8.3 Hz), 5.56–5.45 (2H,m), 5.13–5.02(2H,m), 4.65(4H,d,J=6.4 Hz), 3.78–3.65(4H,m), 3.58–3.46(2H,m), 2.63–2.54(2H,m), 2.53–2.44(4H,m), 2.16–2.00(8H,m), 1.74(3H,s), 1.72(3H,s), 1.67 (6H,s), 1.60(6H,s).

#### Example 37

In a manner identical to Example 45, 2,4-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine(0.70 ml), thereby yielding 2.21 g(82%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 8.24–8.12(2H,m), 6.59(1H,d, J=8.8 Hz), 6.50(1H,s), 5.54–5.43(2H,m), 5.09–5.07(2H,m), 4.64(2H,d,J=6.4 Hz), 4.54(2H,d,J=6.8 Hz), 3.24–3.18(4H, m), 3.56(2H,q,J=6.4 Hz), 2.56(2H,t,J=6.4 Hz), 2.15–2.05 (8H,m), 1.74(6H,s), 1.68–1.67(6H,m).

#### Example 38

In a manner identical to Example 45, 3,5-digeranyloxybenzoic acid(2.13 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine(0.70 ml), thereby yielding 1.67 g(62%) of the aimed compound.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 6.92(2H,d,J=2.0 Hz), 6.61 (1H,s), 5.49(2H,t,J=6.4 Hz), 5.12–5.04(2H,m), 4.54 (4H,d,

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J=6.8 Hz). 3.72(4H,t,J=4.9 Hz), 3.58(2H,q,J=5.9 Hz), 2.58 (2H,t,J=6.3 Hz), 2.53–2.48(4H,m), 2.17–2.04(8H,m), 1.73 (6H,s), 1.68(6H,s), 1.60(6H,s).

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### Example 39

In a manner identical to Example 45, 3,4,5-triprenyloxybenzoic acid(14.98 g) was subjected to a condensation reaction with 1-(2-aminoethyl)morphorine(5.73 g), thereby yielding 13.54 g(70%) of the aimed compound.  
10 m.p. 72.0°–75.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.00(2H, s), 6.60(1H,s), 5.57–5.41(3H,m), 4.62–4.45(6H,m), 3.75–3.63 (4H,m), 3.56–3.45(2H,m), 2.62–2.53(2H,m), 2.52–2.40(4H,m), 1.78–1.55(18H,m).

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### Example 40

In a manner identical to Example 45, 2-geranyloxy-5-methoxybenzoic acid (1.52 g) was subjected to a condensation reaction with 1-(2-aminoethyl) morphorine(0.70 ml), thereby yielding 1.93 g(93%) of the aimed compound.  
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$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 8.45(1H,bs), 7.76(1H,d,J=3.0 Hz), 7.06–6.82(2H,m), 5.77–5.50(1H,m), 5.10–4.94(1H,m), 4.67(2H,d,J=6.8 Hz), 3.81(3H,s), 3.73–3.48(6H,m), 2.61–2.39 (6H,m), 2.14–1.92(4H,m), 1.73(3H,s), 1.67(3H, s), 1.60(3H,s).

### Example 41

In a manner identical to Example 45, 3,5-dimethoxy-4-prenyloxybenzoic acid (0.80 g) was subjected to a condensation reaction with 1-(2-aminoethyl) morphorine(0.42 g), thereby yielding 0.96 g(85%) of the aimed compound.  
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m.p. 116.0°–118.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.00 (2H,s), 6.66(1H,s), 5.57–5.53(1H,m), 4.54(2H,d,J=7.3 Hz), 3.89(6H,s), 3.72(4H,t,J=4.7 Hz), 3.57–3.52(2H,m), 2.61 (2H,t,J=6.4 Hz), 2.51(4H,d,J=4.9 Hz), 1.74 (3H,s), 1.68(3H, s).

### Example 42

40 In a manner identical to Example 45, 3,5-dimethoxy-4-geranyloxybenzoic acid (0.80 g) was subjected to a condensation reaction with 1-(2-aminoethyl) morphorine(0.31 g), thereby yielding 0.74 g(69%) of the aimed compound.

45 m.p. 86.0°–89.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 6.99(2H, s), 6.68(1H,s), 5.59–5.50(1H,m), 5.12–5.03(1H,m), 4.57 (2H,d,J=7.3 Hz), 3.89(6H,s), 3.76–3.67(4H,m), 3.60–3.55 (2H,m), 2.65–2.58(2H,m), 2.57–2.47(4H,m), 2.13–1.98(4H, m), 1.66(3H,s), 1.65(3H,s), 1.58(3H,s).

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### Example 43

In a manner identical to Example 45, 3,5-dimethoxy-4-neryloxybenzoic acid (1.10 g) was subjected to a condensation reaction with 1-(2-aminoethyl) morphorine(0.43 g), thereby yielding 1.46 g(99%) of the aimed compound.  
55

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.00(2H,s), 6.68–6.78(1H,bs), 5.56(1H,t,J=5.4 Hz), 5.08(1H,t,J=5.4 Hz), 4.54 (2H,d,J=6.8 Hz), 3.89(6H,s), 3.74–3.71(4H,m), 3.57–3.53(2H,m), 2.62 (2H,t,J=6.4 Hz), 2.53(4H,t,J=4.4 Hz), 2.14–2.01(4H,m), 1.75(3H,s), 1.67(3H,s), 1.58(3H,s).

### Example 44

In a manner identical to Example 45, 4,5-dimethoxy-3-geranyloxybenzoic acid (1.34 g) was subjected to a condensation reaction with 1-(2-aminoethyl) morphorine(0.58 ml), thereby yielding 0.80 g(45%) of the aimed compound.  
65

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.04(2H.s), 6.94–6.86(1H.bs), 5.51(1H.t, J=5.4 Hz), 5.08(1H.t, J=5.4 Hz), 4.63 (2H.d, J=6.4 Hz), 3.89(6H.s), 3.73–3.69(4H.m), 3.57–3.52(2H.m), 2.61 (2H.t, J=5.8 Hz), 2.56–2.48(4H.m), 2.17–2.04(4H.m), 1.74 (3H.s), 1.66(3H.s), 1.60(3H.s).

#### Example 45

To a solution of 4-geranyloxybenzoic acid(1.92 g) in chloroform(30 ml) were added triethylamine(2.09 ml) and diphenylphosphinic chloride(1.43 ml) while being cooled with ice. After being stirred for 30 minutes, the mixture, with 4-(2-aminoethyl)-1-ethylpiperazine(1.48 g) added thereto, was stirred for 2 hours at room temperature. The reaction mixture was washed with saturated sodium hydrogen carbonate aqueous solution and saturated brine successively, dried over sodium sulfate anhydride, and then concentrated under a vacuum. The residue was purified by silica gel column chromatography (chloroform:methanol=15:1). The resulting solid was recrystallized from hexane, thereby yielding 0.84 g(41%) of the aimed compound.

m.p. 65.2°–66.9° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.93(2H, d, J=8.8 Hz), 6.75(1H, s), 5.48(1H, t, J=6.4 Hz), 5.09(1H, t, J=6.8 Hz), 4.58(2H, d, J=6.4 Hz), 3.27(2H, q, J=5.8 Hz), 2.62–2.20(12H, m), 2.19–2.04(4H, m), 1.74(3H, s), 1.67(3H, s), 1.60(3H, s), 1.10(3H, t, J=6.3 Hz).

#### Example 46

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-isobutylpiperazine (1.19 g), thereby yielding 0.75 g(42%) of the aimed compound.

m.p. 74.0°–75.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.94(2H, d, J=8.8 Hz), 6.78(1H, s), 5.48(1H, t, J=6.8 Hz), 5.09(1H, t, J=6.4 Hz), 4.58(2H, d, J=6.4 Hz), 3.52(2H, q, J=5.4 Hz), 2.59(2H, t, J=5.8 Hz), 2.53(4H, s), 2.43(4H, s), 2.19–2.04(6H, m), 1.77 (1H, n, J=6.8 Hz), 1.74 (3H, s), 1.68(3H.s), 1.60(3H, s), 0.89(6H, d, J=6.8 Hz).

#### Example 47

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-isoamylpiperazine (1.19 g), thereby yielding 0.73 g(40%) of the aimed compound.

m.p. 75.0°–76.8° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.94(2H, d, J=8.8 Hz), 6.73(1H, s), 5.48(1H, t, J=6.1 Hz), 5.14–5.04(1H, m), 4.58(2H, d, J=6.8 Hz), 3.53(2H, q, J=5.4 Hz), 2.61–2.33 (10H, m), 2.19–2.04(4H, m), 1.74 (3H, s), 1.68(3H.s), 1.65–1.55(6H.m), 1.42–1.36 (2H, m), 0.90(2H, d, J=6.4 Hz).

#### Example 48

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-neopenylpiperazine (1.49 g), thereby yielding 0.64 g(28%) of the aimed compound.

m.p. 72.0°–73.4° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.94(2H, d, J=8.8 Hz), 6.76(1H, s), 5.48(1H, t, J=6.4 Hz), 5.09(1H, t, J=6.4 Hz), 4.58(2H, d, J=6.8 Hz), 3.52(2H, q, J=5.9 Hz), 2.58–2.48(10H, m), 2.17–2.06(6H, m), 1.74(3H, s), 1.68(3H.s), 1.61(3H.s), 0.86(9H, s).

#### Example 49

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.65 g) was subjected to a con-

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densation reaction with 4-(2-aminoethyl)-1-(2-ethylbutyl) piperazine(1.91 g). thereby yielding 1.01 g(36%) of the aimed compound.

5 m.p. 59.3°–60.1° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H. d.  $J=8.8$  Hz). 6.94(2H. d.  $J=8.8$  Hz). 6.74(1H. s). 5.48(1H. t.  $J=6.1$  Hz). 5.09(1H. t.  $J=6.8$  Hz). 4.58(2H. d.  $J=6.4$  Hz). 3.52(2H. q.  $J=5.4$  Hz). 2.58(2H. t.  $J=5.8$  Hz). 2.51(2H. s). 2.43(4H. s). 2.16–2.07(6H. m). 1.74(3H. s). 1.68(3H. s). 1.61(3H. s). 1.45–1.24(5H. m). 0.86(6H. t.  $J=7.5$  Hz).

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### Example 50

In a manner identical to Example 45. 4-geranyloxybenzoic acid(1.88 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-n-butylpiperazine (3.04 g). thereby yielding 1.29 g(46%) of the aimed compound.

15 m.p. 64.3°–65.9° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H. d.  $J=8.8$  Hz). 6.94(2H. d.  $J=8.8$  Hz). 6.70(1H. s). 5.48(1H. t.  $J=5.9$  Hz). 5.09(1H. t.  $J=6.8$  Hz). 4.58(2H. d.  $J=6.8$  Hz). 20 3.52(2H. q.  $J=5.4$  Hz). 2.61–2.40(8H. m). 2.34(2H. t.  $J=7.8$  Hz). 2.28–2.07(4H. m). 1.74 (3H. s). 1.68(3H. s). 1.61 (3H. s). 1.54–1.44(2H. m). 1.37–1.27(2H. m). 0.92(3H. t.  $J=7.3$  Hz).

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### Example 51

In a manner identical to Example 45. 4-geranyloxybenzoic acid(1.92 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(2-ethylhexyl) piperazine(2.03 g). thereby yielding 1.46 g(42%) of the aimed compound.

30 m.p. 48.0°–49.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H. d.  $J=8.8$  Hz). 6.94(2H. d.  $J=8.8$  Hz). 6.74(1H. s). 5.48(1H. t.  $J=5.9$  Hz). 5.09(1H. t.  $J=6.8$  Hz). 4.58(2H. d.  $J=6.8$  Hz). 35 3.51(2H. q.  $J=5.9$  Hz). 2.58(2H. t.  $J=6.1$  Hz). 2.50–2.42(8H. m). 2.19–2.04(4H. m). 1.78 (3H. s). 1.68(3H. s). 1.61(3H. s). 1.46–1.26(9H. m). 0.91–0.83(6H. m).

### Example 52

40 In a manner identical to Example 45. 4-geranyloxybenzoic acid(1.37 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-phenylpiperazine (1.54 g). thereby yielding 1.57 g(68%) of the aimed compound.

45 m.p. 154.0°–156.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H. d.  $J=8.8$  Hz). 7.30–7.22(2H. m). 6.95–6.92(4H. m). 6.87(1H. t.  $J=6.8$  Hz). 6.73(1H. s). 5.47(1H. t.  $J=6.8$  Hz). 5.08(1H. t.  $J=6.8$  Hz). 4.58(2H. d.  $J=6.4$  Hz). 3.58(1H. q.  $J=5.4$  Hz). 2.67(6H. t.  $J=5.8$  Hz). 2.19–2.04(4H. m). 1.74 50 (3H. s). 1.67(3H. s). 1.60(3H. s).

### Example 53

In a manner identical to Example 45. 4-geranyloxybenzoic acid(1.92 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(4-methoxyphenyl) piperazine(3.01 g). thereby yielding 2.85 g(70%) of the aimed compound.

55 m.p. 159.0°–160.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73(2H. d.  $J=8.8$  Hz). 6.90–6.83(6H. m). 6.73(1H. s). 5.48(1H. t.  $J=6.8$  Hz). 5.09(1H. t.  $J=6.4$  Hz). 4.58(2H. d.  $J=6.4$  Hz). 3.77(3H. s). 3.57(2H. q.  $J=5.8$  Hz). 3.12 (4H. t.  $J=4.9$  Hz). 2.68(6H. t.  $J=5.4$  Hz). 2.19–2.04(4H. m). 1.74 (3H. s). 1.67(3H. s). 1.60 (3H. s).

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### Example 54

In a manner identical to Example 45. 4-geranyloxybenzoic acid(2.80 g) was subjected to a con-

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densation reaction with 4-(2-aminoethyl)-1-(isopropylcarbamoyl methyl)piperazine (1.98 g), thereby yielding 2.21 g(65%) of the aimed compound as pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.72(2H, d, J=8.8 Hz), 6.94 (2H, d, J=8.8 Hz), 6.91(1H, s), 6.69(1H, s), 5.48 (1H, t, J=6.4 Hz), 5.09(1H, t, J=6.8 Hz), 4.58(2H, d, J=6.8 Hz), 4.10(1H, d, J=5.4 Hz), 3.54(2H, q, J=5.8 Hz), 2.98(2H, s), 2.61(4H, t, J=5.8 Hz), 2.56(6H, s), 2.19–2.04(4H, m), 1.74 (3H, s), 1.67(3H,s), 1.60(3H, s), 1.17(6H, d, J=6.8 Hz).

### Example 55

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.65 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(pyrоридинкарбонил methyl)piperazine (2.86 g), thereby yielding 1.22 g(41%) of the aimed compound as pale yellow oil.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.92 (2H, d, J=8.8 Hz), 6.84(1H, s), 5.48(1H, t, J=5.4 Hz), 5.09(1H, t, J=5.8 Hz), 4.58(2H, d, J=6.4 Hz), 3.54(2H, q, J=5.4 Hz), 3.52–3.40(4H, m), 3.14(2H, s), 2.73–2.39(10H, m), 2.19–2.04(4H, m), 1.95 (2H, q, J=6.8 Hz), 1.85(2H, q, J=6.8 Hz), 1.75(3H, s), 1.68(3H,s), 1.61(3H, s).

### Example 56

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.65 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-benzylpiperazine (1.97 g), thereby yielding 2.14 g(75%) of the aimed compound.

m.p. 80.0°–81.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.72(2H, d, J=8.8 Hz), 7.32–7.23(5H, m), 6.94(2H, d, J=8.8 Hz), 6.72(1H, s), 5.48(1H, t, J=6.4 Hz), 5.09(1H, t, J=6.8 Hz), 4.59(2H, d, J=6.4 Hz), 3.52(2H, s), 3.51 (2H, q, J=5.8 Hz), 2.59(6H, t, J=5.8 Hz), 2.52(4H, s), 2.19–2.04(4H, m), 1.75 (3H, s), 1.68(3H,s), 1.61(3H, s).

### Example 57

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(4-fluorobenzyl) piperazine (1.63 g), thereby yielding 1.12 g(57%) of the aimed compound.

m.p. 95.0°–96.0° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.72(2H, d, J=8.8 Hz), 7.32–7.26(2H, m), 7.02–6.96(2H, m), 6.94(2H, d, J=8.8 Hz), 6.70(1H, s), 5.48(1H, t, J=6.4 Hz), 5.09(1H, t, J=6.4 Hz), 4.59(2H, d, J=6.4 Hz), 3.52(2H, q, J=5.8 Hz), 3.48(2H, s), 2.59(2H, t, J=5.8 Hz), 2.58–2.30(8H, m), 2.19–2.04(4H, m), 1.75 (3H, s), 1.68(3H,s), 1.61(3H, s).

### Example 58

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(3,4-methylenedioxybenzyl)piperazine(1.36 g), thereby yielding 0.96 g(46%) of the aimed compound.

m.p. 90.8°–92.5° C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ (ppm) 7.73(2H, d, J=8.8 Hz), 6.94(2H, d, J=8.8 Hz), 6.85(1H, s), 6.74(2H, d, J=1.0 Hz), 5.94(2H, s), 5.48(1H, t, J=6.4 Hz), 5.09(1H, t, J=6.8 Hz), 4.58(2H, d, J=6.4 Hz), 3.52(2H, q, J=5.4 Hz), 3.43(2H, s), 2.64–2.34(10H, m), 2.19–2.04(4H, m), 1.75 (3H, s), 1.68(3H,s), 1.61(3H, s).

### Example 59

In a manner identical to Example 45, 4-geranyloxybenzoic acid(1.65 g) was subjected to a con-

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densation reaction with 4-(2-aminoethyl)-1-(2-benzothiazolyl) piperazine(1.88 g), thereby yielding 2.30 g(74%) of the aimed compound.

5 m.p. 136.0°–138.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.33 (2H. d,  $J=8.8$  Hz), 7.61(1H. d,  $J=6.4$  Hz), 7.56(1H. d,  $J=7.8$  Hz), 7.30(1H. t,  $J=6.8$  Hz), 7.09(1H. t,  $J=6.8$  Hz), 6.94(2H. d,  $J=8.8$  Hz), 6.33(1H. s), 5.47(1H. t,  $J=6.4$  Hz), 5.08(1H. t,  $J=6.8$  Hz), 4.58(2H. d,  $J=6.4$  Hz), 3.68(4H. t,  $J=4.9$  Hz), 3.59(2H. q,  $J=5.4$  Hz), 2.82–2.04(6H.m), 2.19–2.04(4H. m), 1.74(3H. s), 1.67(3H. s), 1.60(3H. s).

### Example 60

In a manner identical to Example 45. 15 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(2-thiazolyl) piperazine (1.34 g), thereby yielding 0.55 g(29%) of the aimed compound.

20 m.p. 121.3°–122.4° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 7.73 (2H. d,  $J=8.3$  Hz), 7.21(1H. d,  $J=3.9$ ), 6.93(2H. d,  $J=8.8$  Hz), 6.65(1H. s), 6.59(1H. d,  $J=3.4$  Hz), 5.47(1H. t,  $J=6.4$  Hz), 5.09(1H. t,  $J=6.8$  Hz), 4.58(2H. d,  $J=6.4$  Hz), 3.58(2H. q,  $J=5.8$  Hz), 3.53(4H. t,  $J=4.9$  Hz), 2.71–2.60(6H. m), 2.19–2.04 (4H. m), 1.74 (3H. s), 1.67(3H.s), 1.60(3H. s).

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### Example 61

In a manner identical to Example 45. 30 4-geranyloxybenzoic acid(1.10 g) was subjected to a condensation reaction with 4-(2-aminoethyl)-1-(2-pyrimidinyl) piperazine(2.00 g), thereby yielding 0.89 g(48%) of the aimed compound.

35 m.p. 106.0°–107.2° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 8.31 (2H. d,  $J=4.4$  Hz), 7.74(2H. d,  $J=8.8$  Hz), 6.92(2H. d,  $J=8.8$  Hz), 6.50(1H. t,  $J=4.9$  Hz), 5.47(1H. t,  $J=6.4$  Hz), 5.09(1H. t,  $J=6.8$  Hz), 4.57(2H. q,  $J=6.8$  Hz), 3.87 (4H. s), 3.60(2H. q,  $J=5.8$  Hz), 2.68(2H. t,  $J=5.8$  Hz), 2.67–2.54(4H. m), 2.19–2.04 (4H. m), 1.74 (3H. s), 1.67(3H.s), 1.60(3H. s).

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### Example 62

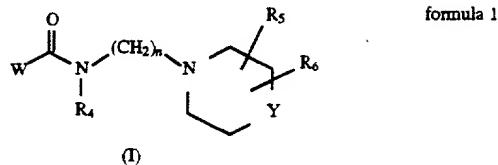
40 4-(4-Fluorobenzoyloxy)-3-isobutylbenzoic acid(2.00 g) was dissolved in methylene chloride(25 ml) and triethylamine(1.73 g), and then diphenylphosphinic chloride (1.75 g) was added thereto while being cooled with ice. After 45 being stirred for 40 minutes, the mixture, with 4-(2-aminoethyl)-1-isobutylpiperazine(1.85 g) added thereto, was stirred overnight at room temperature. The reaction mixture was washed with water, dried over magnesium sulfate, and then filtrated. The filtrate was concentrated 50 under a vacuum and the residue was purified by silica gel column chromatography (chloroform:methanol=20:1). The resulting solid was recrystallized from n-hexane, thereby yielding 0.95 g of colorless crystals. The crystals was dissolved in chloroform and then 1N hydrochloric acid ether 55 solution was added thereto. The reaction mixture was stirred at room temperature for 10 minutes. The depositing solid was collected by filtration and recrystallized from ethanol/ethyl acetate mixed solution, thereby yielding 1.03 g(29%) of the aimed compound as white crystals.

60 m.p. 173.0°–174.0° C.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$  (ppm) 13.03(1H. s), 8.13(1H. s), 7.87(1H. d,  $J=8.8$  Hz), 7.83(1H. s), 7.38(2H. t,  $J=5.8$  Hz), 7.08(2H. t,  $J=8.8$  Hz), 6.91(1H. d,  $J=8.8$  Hz), 5.07(2H. s), 4.50–4.30(2H. bs), 4.04–3.96(2H. m), 3.90(2H. s), 3.64(4H. t,  $J=14.7$  Hz), 3.40(2H. s), 2.94(2H. d,  $J=6.4$  Hz), 2.55(2H. d,  $J=4.9$  Hz), 2.01–1.91(1H. m), 1.88–1.71 (1H. m), 1.15(6H. d,  $J=6.8$  Hz), 0.89(6H. d,  $J=6.8$  Hz).

What is claimed is:

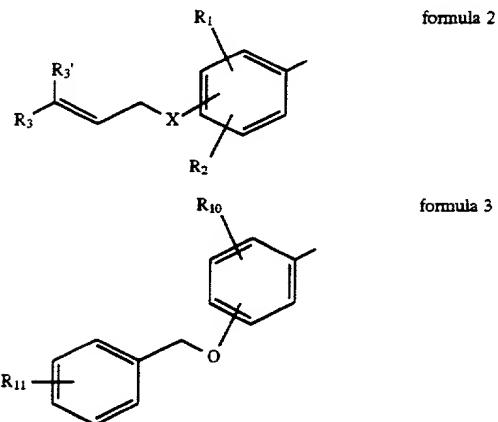
53

1. An alkylendiamine derivative or a salt thereof expressed by the following formula 1:



(I)

wherein W represents a group expressed by the following formula 2 or formula 3;



wherein each of R<sub>1</sub> and R<sub>2</sub> represents hydrogen atom, a lower alkoxy group, an alkenyloxy group, or a halogen atom:

each of R<sub>3</sub> and R<sub>3'</sub> represents methyl group, [prenyl] prenyl-CH<sub>2</sub> group, or [geranyl] geranyl-CH<sub>2</sub> group and when one of R<sub>3</sub> and R<sub>3'</sub> is [prenyl] prenyl-CH<sub>2</sub> group or [geranyl] geranyl-CH<sub>2</sub> group, another is methyl group;

X represents oxygen atom or sulfur atom;

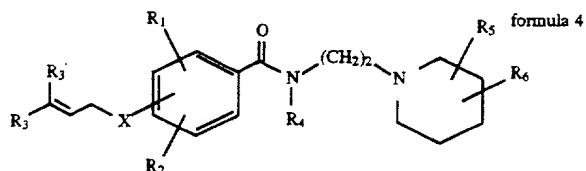
R<sub>10</sub> represents a lower alkyl group; and

R<sub>11</sub> represents a halogen atom; and wherein each of R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> represents hydrogen atom or a lower alkyl group;

Y represents a group expressed by —CH<sub>2</sub>—, —O—, or —N(R<sub>7</sub>)—, while R<sub>7</sub> represents a lower alkyl group, an aryl group, a carbamoyl lower alkyl group, an aralkyl group, or a heterocyclic group having 5 to 9 members; and

n represents an integer of 1 to 6.

2. An alkylendiamine derivative or a salt thereof according to claim 1, which expressed by the following formula 4.



wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3'</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and X are same as those in the above-mentioned formula 1.

3. An alkylenediamine derivative or a salt thereof according to claim 2, wherein X is oxygen atom, while R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen atoms.

4. An alkylenediamine derivative or a salt thereof according to claim 3, wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

5. An alkylenediamine derivative or a salt thereof according to claim 3, wherein R<sub>1</sub> and/or R<sub>2</sub> is an alkenyloxy group expressed by the following formula 5;

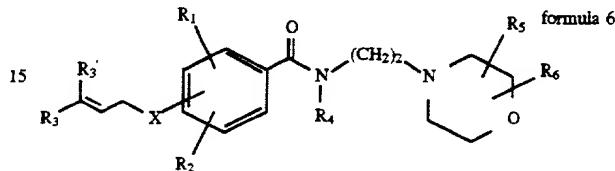
54



wherein each of R<sub>b</sub> and R<sub>b'</sub> represents methyl group, [prenyl] prenyl-CH<sub>2</sub> group, or [geranyl] geranyl-CH<sub>2</sub> group and when one of R<sub>b</sub> and R<sub>b'</sub> is [prenyl] prenyl-CH<sub>2</sub> group or [geranyl] geranyl-CH<sub>2</sub> group, another is methyl group.

6. An alkylenediamine derivative or a salt thereof according to claim 3, wherein R<sub>1</sub> and/or R<sub>2</sub> is a lower alkoxy group.

10 7. An alkylenediamine derivative or a salt thereof according to claim 1, which expressed by the following formula 6.



20 wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3'</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and X are same as those in the above-mentioned formula 1.

8. An alkylenediamine derivative or a salt thereof according to claim 7, wherein X is oxygen atom, while R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are hydrogen atoms.

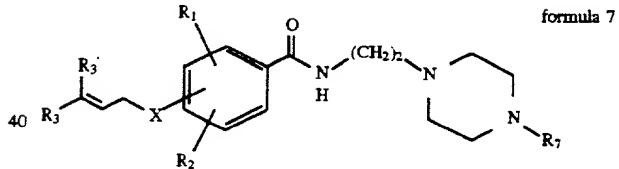
25 9. An alkylenediamine derivative or a salt thereof according to claim 8, wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

10. An alkylenediamine derivative or a salt thereof according to claim 8, wherein R<sub>1</sub> and/or R<sub>2</sub> is an alkenyloxy group expressed by above-mentioned formula 5.

30 11. An alkylenediamine derivative or a salt thereof according to claim 8, wherein R<sub>1</sub> and/or R<sub>2</sub> is a lower alkoxy group.

12. An alkylenediamine derivative or a salt thereof according to claim 1, which expressed by the following formula 7:

35

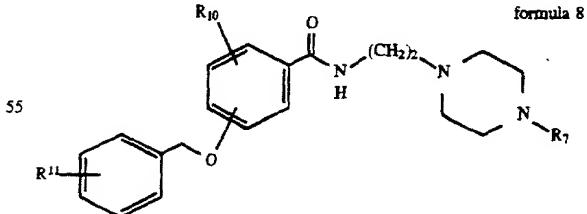


wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>3'</sub>, R<sub>7</sub>, and X are same as those in the above-mentioned formula 1.

45 13. An alkylenediamine derivative or a salt thereof according to claim 12, wherein X is oxygen atom, while R<sub>1</sub> and R<sub>2</sub> are hydrogen atoms.

14. An alkylendiamine derivative or a salt thereof according to claim 1, which expressed by the following formula 8:

50



60 wherein R<sub>7</sub> is a lower alkyl group; and R<sub>10</sub> and R<sub>11</sub> are same as those in the above-mentioned formula 3.

15. An alkylendiamine derivative or a salt thereof according to claim 14, wherein R<sub>7</sub> and R<sub>10</sub> are isobutyl groups.

65 16. An alkylendiamine derivative or a salt thereof according to claim 14 or 15, wherein R<sub>11</sub> is fluorine atom bonded to para-position.

## 55

17. An anti-ulcer drug comprising, as an effective ingredient, an alkylendiamine derivative or a pharmacologically acceptable salt thereof according to claim 1, together with a pharmaceutically acceptable carrier and/or adjuvant.

18. An antibacterial drug against *Helicobacter pylori* comprising, as an effective ingredient, an alkylendiamine derivative or a pharmacologically acceptable salt thereof according to claim 1, together with a pharmaceutically acceptable carrier and/or adjuvant.

19. A method for the treatment of peptic ulcers in man or mammals, which comprises administering an effective amount of an alkylendiamine derivative or a pharmacologically acceptable salt thereof according to claim 1 to a host.

20. A method according to claim 19, wherein said peptic ulcers are gastric ulcers in man.

21. A method for the inhibition of acid secretion in stomach of man or mammals, which comprises administering an effective amount of an alkylendiamine derivative or

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a pharmacologically acceptable salt thereof according to claim 1 to a host.

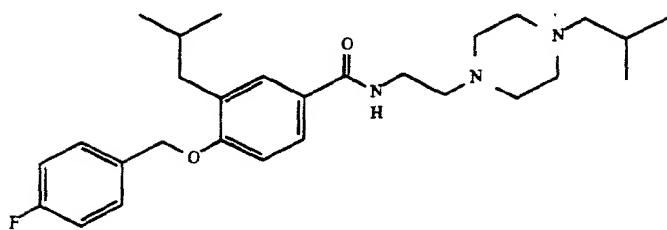
22. A method for the inhibition of growth of *Helicobacter pylori* in stomach of man or mammals, which comprises administering an effective amount of an alkylendiamine derivative or a pharmacologically acceptable salt thereof according to claim 1 to a host.

23. A method for the prevention of peptic ulcers in man or mammals, which comprises administering an effective amount of an alkylendiamine derivative or a pharmacologically acceptable salt thereof according to claim 1 to a host.

24. A method according to claim 23, wherein said peptic ulcers are gastric ulcers in man.

25. An alkylendiamine derivative or a salt thereof according to claim 14, wherein R<sub>10</sub> and —O—(CH<sub>2</sub>)—C<sub>6</sub>H<sub>4</sub>—R<sub>11</sub> are at positions 3 and 4 of the benzene ring.

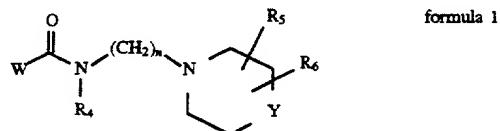
26. An alkylene diamine derivative or a salt thereof having the following formula:



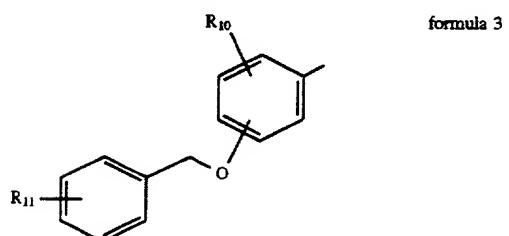
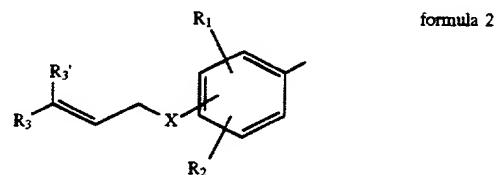
\* \* \* \*

The invention provides a compound which has anti-ulcer

effect and antibacterial activity against *Helicobacter pylori*. This compound is an alkylendiamine derivative or salt which has a general formula of (1):



wherein each of R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> is hydrogen or lower alkyl; n represents an integer of 1 to 6; Y is —CH<sub>2</sub>—, —O—, or —N(R<sub>7</sub>)—, wherein R<sub>7</sub> is lower alkyl, aryl, carbamoyl lower alkyl, aralkyl, or a heterocyclic group having 5 to 9 carbon numbers; and, W is a group expressed by formulas 2 or 3:

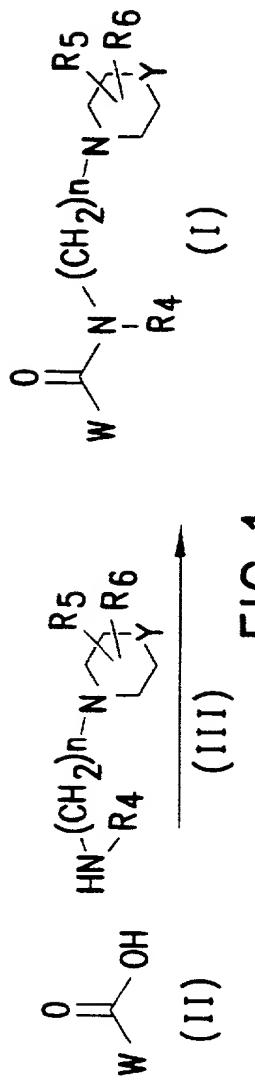


wherein (1) in formula 2: each of R<sub>sub.1</sub> and R<sub>sub.2</sub> is hydrogen, lower alkoxy, alkenyloxy, or a halogen atom; each of R<sub>sub.3</sub> and R<sub>sub.3</sub> is methyl, [prenyl] prenyl-CH<sub>2</sub>, or [geranyl] geranyl-CH<sub>2</sub>; when one of R<sub>sub.3</sub> and R<sub>sub.3</sub> is [prenyl] prenyl-CH<sub>2</sub> or [geranyl] geranyl-CH<sub>2</sub>, the other must be a methyl group; and X is oxygen or sulfur; and (2) in formula 3, R<sub>sub.10</sub> is a lower alkyl, and R<sub>sub.11</sub> is a halogen atom.

This application is a reissue

application for U.S. Patent No.  
5,814,634 issued on September  
29, 1998 for U.S. Serial No.  
08/842,891 filed on April 17,  
1997.

## REACTION FORMULA A;



**FIG. 1**

## REACTION FORMULA B;

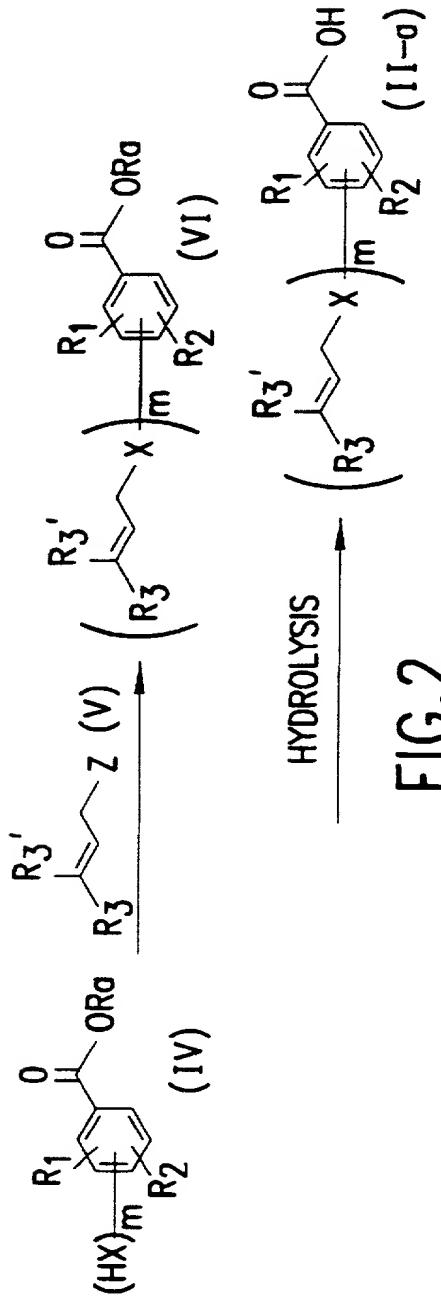


FIG. 2

REACTION FORMULA C;

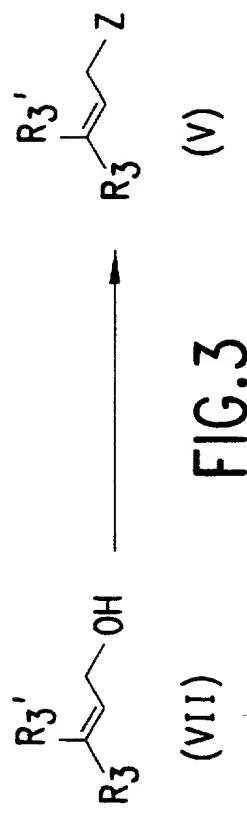


FIG.3

REACTION FORMULA D;

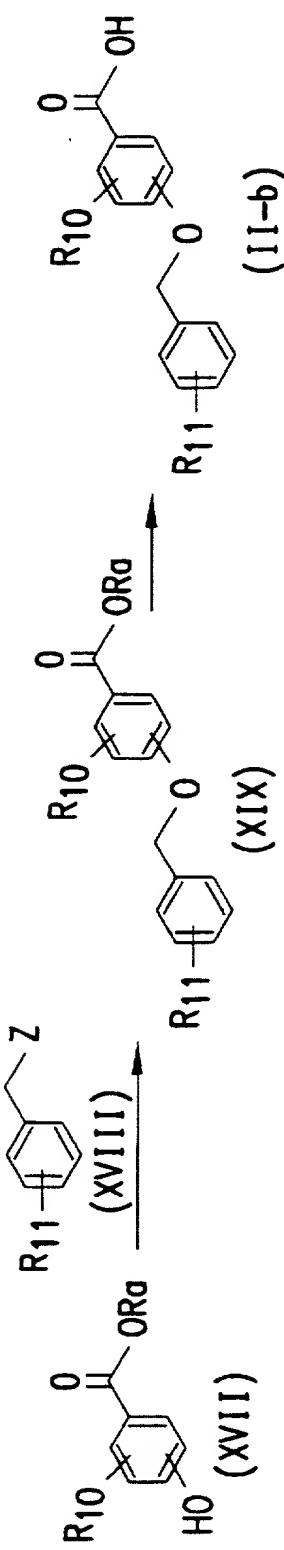
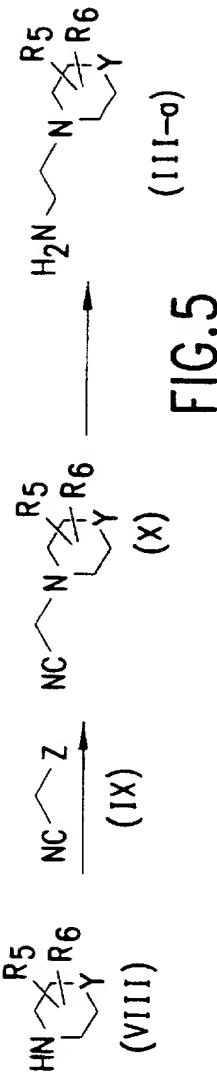
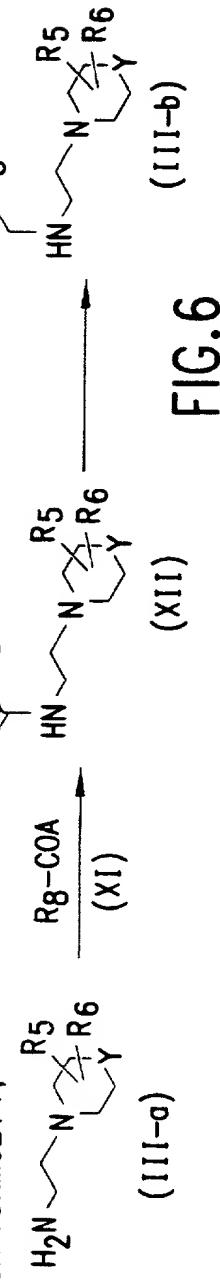


FIG.4

REACTION FORMULA E;



REACTION FORMULA F;



REACTION FORMULA G;

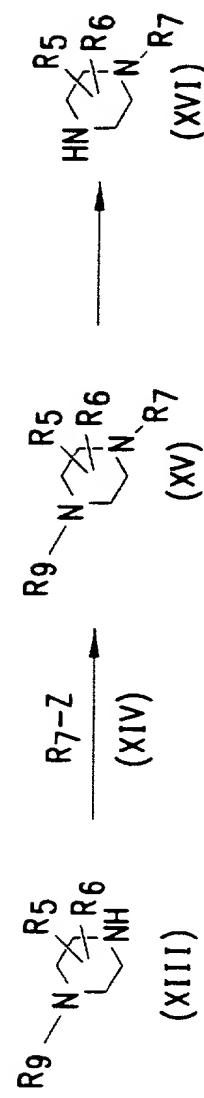


FIG.7

FIG.5

(III- $\alpha$ )

FIG.6

(XII)

(III- $\beta$ )

FIG.6

(XV)

(XVI)



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RONALD R. SNIDER  
P.O. BOX 27613  
WASHINGTON, D.C. 20038-7613



\*100516403A\*

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RECORDATION DATE: 04/17/1997

REEL/FRAME: 8533/0020

NUMBER OF PAGES: 3

BRIEF: ASSIGNMENT OF ASSIGNOR'S INTEREST (SEE DOCUMENT FOR DETAILS).

ASSIGNOR:

NISHINO, CHIKAO

DOC DATE: 04/10/1997

ASSIGNOR:

SATO, FUMITAKA

DOC DATE: 04/10/1997

ASSIGNOR:

UETAKE, TOMOHIRO

DOC DATE: 04/10/1997

ASSIGNOR:

FUKUNISHI, HIROTADA

DOC DATE: 04/10/1997

ASSIGNOR:

KOJIMA, NAO

DOC DATE: 04/10/1997

ASSIGNEE:

SHISEIDO CO., LTD.  
5-5 GINZA 7-CHOME, CHUO-KU  
TOKYO 104-10, JAPAN

8533/0020 PAGE 2

SERIAL NUMBER: 08842891  
PATENT NUMBER:

FILING DATE:  
ISSUE DATE:

JACQUELINE MOORE, PARALEGAL  
ASSIGNMENT DIVISION  
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70996 U.S. PTO  
04/17/97

08-25-1997

100516403

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08/842891

1. Name of conveying party(ies):

1. Chikao NISHINO

Additional name(s) of conveying party(ies) attached?  Yes  No

3. Nature of conveyance:

Assignment Merger

Security Agreement Change of Name

Other:

Execution Date: April 10, 1997

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: April 10, 1997

A. Patent Application No.(s)

B. Patent No.(s)

\*

\*

Additional numbers attached?  Yes  No

5. Name and address of party to whom correspondence concerning document should be mailed:

Ronald R. Snider  
P.O. Box 27613  
Washington, D.C. 20038-7613  
(202-347-2600)

06/1997 DNASH1 00000010 08842891  
FC:581 40.00 OP

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41): \$40.00

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April 17, 1997

Date

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# ASSIGNMENT

SOLE/JOINT INVENTION  
(U.S. Rights Only)

IWA-126

WHEREAS I/We, the below named inventor(s), [hereinafter referred to as Assignor(s)], have made an invention entitled:  
ALKYLENDIAMINE DERIVATIVE, ANTI-ULCER DRUG, AND ANTIBACTERIAL DRUG

(Title of Invention)

for which I/We executed an application for United States Letters Patent concurrently herewith or filed an application for United States Letters Patent on \_\_\_\_\_, 19 \_\_\_\_ (Serial No. \_\_\_\_\_); and  
WHEREAS, SHISEIDO CO., LTD.

(Full Name of Assignee)

a corporation of JAPAN

(Country of Incorporation)

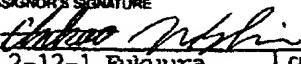
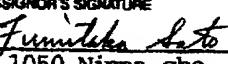
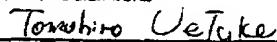
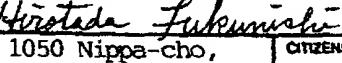
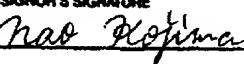
whose post office address is 5-5 Ginza 7-chome, Chuo-ku, TOKYO 104-10 JAPAN

(hereinafter referred to as Assignee), is desirous of securing the entire right, title, and interest in and to this invention, the application for United States Letters Patent on this invention and the Letters Patent to be issued upon this application;

NOW THEREFORE, be it known that, for good and valuable consideration the receipt of which from assignee is hereby acknowledged, I/We, as assignor(s), have sold, assigned, transferred, and set over, and do hereby sell, assign, transfer, and set over unto the assignee, its lawful successors and assigns, my/our entire right, title, and interest in and to this invention and this application, and all divisions, and continuations thereof, and all Letters Patent of the United States which may be granted thereon, and all reissues thereof; and I/We hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue all Letters Patent for this invention to assignee, its successors and assigns, in accordance with the terms of this Assignment;

AND, I/WE HEREBY further covenant and agree that I/We will, without further consideration, communicate with assignee, its successors and assigns, any facts known to me/us respecting this invention and testify in any legal proceeding, sign all lawful papers when called upon to do so, execute and deliver all papers that may be necessary or desirable to perfect the title to this invention in said assignee, its successors and assigns, execute all divisional, continuation, and reissue applications, make all rightful oaths and generally do everything possible to aid assignee, its successors and assigns, to obtain and enforce proper patent protection for this invention in the United States, it being understood that any expense incident to the execution of such papers shall be borne by the assignee, its successors and assigns.

IN TESTIMONY WHEREOF, I/We have hereunto set our hand(s).

1. FULL NAME OF SOLE OR FIRST ASSIGNOR Chikao NISHINO	ASSIGNOR'S SIGNATURE 	DATE April 10, 1997
ADDRESS c/o SHISEIDO RESEARCH CENTER(2), 2-12-1 Fukuura, Kanazawa-ku, Yokohama-shi, KANAGAWA 236 JAPAN	CITIZENSHIP JAPANESE	
2. FULL NAME OF SECOND ASSIGNOR, IF ANY Fumitaka SATO	ASSIGNOR'S SIGNATURE 	DATE April 10, 1997
ADDRESS c/o SHISEIDO RESEARCH CENTER(1), 1050 Nippa-cho, Kohoku-ku, Yokohama-shi, KANAGAWA 223 JAPAN	CITIZENSHIP JAPANESE	
3. FULL NAME OF THIRD ASSIGNOR, IF ANY Tomohiro UETAKE	ASSIGNOR'S SIGNATURE 	DATE April 10, 1997
ADDRESS 10-2 Sotokanda 4-chome, Chiyoda-ku, TOKYO 101 JAPAN	CITIZENSHIP JAPANESE	
4. FULL NAME OF FOURTH ASSIGNOR, IF ANY Hirotada FUKUNISHI	ASSIGNOR'S SIGNATURE 	DATE April 10, 1997
ADDRESS c/o SHISEIDO RESEARCH CENTER(1), 1050 Nippa-cho, Kohoku-ku, Yokohama-shi, KANAGAWA 223 JAPAN	CITIZENSHIP JAPANESE	
5. FULL NAME OF FIFTH ASSIGNOR, IF ANY Naotaka KOJIMA	ASSIGNOR'S SIGNATURE 	DATE April 10, 1997
ADDRESS c/o SHISEIDO CO., LTD. 5-5 Ginza 7-chome, Chuo-ku, TOKYO 104-10 JAPAN	CITIZENSHIP JAPANESE	
6. FULL NAME OF SIXTH ASSIGNOR, IF ANY	ASSIGNOR'S SIGNATURE	DATE
ADDRESS	CITIZENSHIP	

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1416

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<b>REISSUE APPLICATION BY THE INVENTOR, OFFER TO SURRENDER PATENT</b>		Docket Number (Optional) IWA-126-USA7
---	--	--

This is part of the application for a reissue patent based on the original patent identified below.

Name of Inventor(s) Chikao Nishino, Fumitaka Sato, Tomohiro Uetake, Hirotada Fukunishi, Naohiko Kojima	
Patent Number 5,814,634	Date Patent Issued September 29, 1998
Title of invention Alkylenediamine Derivative Antiulcer Drug and Antibacterial Drug	

I am the inventor of the original patent.

I offer to surrender the original patent.

1.  Filed herein is a certificate under 37 CFR 3.73(b).

2.  Ownership of the patent is in the inventor(s), and no assignment of the patent has been made.

One of boxes 1 or 2 above must be checked.

The written consent of all assignees owning an undivided interest in the original patent is included in this application for reissue.

Signature	Date
-----------	------

Typed or printed name	
-----------------------	--

The assignee owning an undivided interest in said original patent is <u>Shiseido Co., Ltd.</u> , and the assignee consents to the accompanying application for reissue.	
---	--

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001 and that such willful false statements may jeopardize the validity of the application, any patent issued thereon, or any patent to which this declaration is directed.

Name of assignee Shiseido Co., Ltd.	
--	--

Signature of person signing for assignee <u>Satoru Takeda</u>	Date 28. Sep. 2000
--	-----------------------

Typed or printed name and title of person signing for assignee Satoru TAKEDA, General Manager	
--	--

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Chikao Nishino et al.

Serial No.: (Reissue Application  
of U.S. Patent No. 5,814,634  
issued on September 29, 1998) Art Unit: 1203

Filed: April 17, 1997 Examiner:

For: Alkylenediamine Derivative, Anti-Ulcer Drug, and  
Antibacterial Drug

Hon. Assistant Commissioner  
for Patents and Trademarks  
Washington, DC 20231

REISSUE APPLICATION DECLARATION  
AND POWER OF ATTORNEY BY INVENTORS

Sir:

We, the named applicants of the above referenced U.S. Patent,  
hereby declare that:

1. Our residences, post office addresses, and citizenships  
are as stated below next to our names.

2. We are the original and joint inventors of the subject  
matter which is described and claimed in U.S. Patent No. 5,814,634  
(hereafter "the '634 patent") granted September 29, 1998, and  
described and claimed in the above-identified reissue application.

3. We have reviewed and understand the contents of the  
specification and claims of the '634 patent and the specification  
and claims of the above-identified reissue application and as  
amended to date.

4. We believe the '634 patent to be wholly or partly  
inoperative or invalid by reason of the patentees claiming less  
than the patentees had the right to claim in said patent and  
because of an error in said patent, which error is described in  
paragraphs 6 through 9 of this Declaration.

5. The errors described in paragraphs 6 through 9 hereof, and all errors being corrected in this reissue application up to the time of filing of this Declaration arose without any deceptive intention on the part of the applicants.

6. During the prosecution of the corresponding European application (Application No. 97 302 666.9; filing date: April 18, 1998) in the European Patent Office (hereafter "the EPO") it was realized that the compounds of claim 1, as originally written, had been inadvertently limited to alkylidendiamine derivatives or salts thereof of a general formula 1 in which "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_3$  and  $R_3'$  is prenyl group or geranyl group, another is methyl group" and that the disclosure of the inventors in the patent was much broader than the scope of the issued claim 1. It was further realized during the prosecution in the EPO, that the compounds of claim 5, as originally written, had been inadvertently limited to alkylidendiamine derivatives or salts thereof of a general formula 4 in which " $R_1$  and/or  $R_2$  is an alkenyloxy group expressed by the...formula 5... wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_b$  and  $R_b'$  is prenyl group or geranyl group, another is methyl group" and that the disclosure of the inventors in the patent was much broader than the scope of the issued claim 5.

7. The error which we seek to cure by reissue is the unintentional omission of one supplementary  $CH_2$  group from (a) the substitutents  $R_3$  and  $R_3'$  of claim 1 and (b) the substitutents  $R_b$  and

$R_b'$  of claim 5.

8. Amended claim 1 now requires in pertinent part that "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl- $CH_2$  group, or geranyl- $CH_2$  group and when one of  $R_3$  and  $R_3'$  is prenyl- $CH_2$  group or geranyl- $CH_2$  group, another is methyl group," in lieu of the former erroneous proviso reciting that "each of  $R_3$  and  $R_3'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_3$  and  $R_3'$  is prenyl group or geranyl group, another is methyl group." Without the proposed amendment, claim 1 provides no coverage for the compounds in which:

- (a)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is  $CH_3-$  and  $R_3'$  is prenyl- $CH_2-$  group when only one neryloxy group is on a benzene ring;
- (b)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is prenyl- $CH_2$  group and  $R_3'$  is methyl group when only one geranyloxy group is on a benzene ring;
- (c)  $R_1$  and  $R_2$  are not alkenyloxy groups,  $R_3$  is geranyl- $CH_2-$  group and  $R_3'$  is methyl group when only one farnesyloxy group is on a benzene ring; and
- (d) one of  $R_1$  and  $R_2$  is geranyloxy,  $R_3$  is prenyl- $CH_2-$  group and  $R_3$  is methyl group when two geranyloxy groups are on a benzene ring.

Such compounds are illustrated in Examples 2-14, 20-26, 29-34, 36-38 and 41-61 of the '634 patent. Thus, this difference is an error related to subject matter which was not previously claimed and, hence, the issued claim 1 does not claim all that we are entitled

to claim in the '634 patent. No new matter is added by this amendment of claim 1.

9. Similarly, amended claim 5 now reads in pertinent part that "wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl- $CH_2$  group, or geranyl- $CH_2$  group and when one of  $R_b$  and  $R_b'$  is prenyl- $CH_2$  group or geranyl- $CH_2$  group, another is methyl group" in lieu of the previous mistaken proviso stating that "wherein each of  $R_b$  and  $R_b'$  represents methyl group, prenyl group, or geranyl group and when one of  $R_b$  and  $R_b'$  is prenyl group or geranyl group, another is methyl group." Without the proposed amendment --because according to the original claim 5  $R_b$  and  $R_b'$  can be neither prenyl- $CH_2$ - group nor geranyl- $CH_2$ - group--claim 5 provides no coverage for the compounds in which each of  $R_1$  and  $R_2$  is alkenyloxy group such as prenyloxy, geranyloxy, neryloxy or farnesyloxy. Such compounds are depicted in Examples 11-14 and 36-38 of the '634 patent. Thus, this difference is an error related to subject matter which was not previously claimed and, hence, the issued claim 5 does not claim all that we are entitled to claim in the '634 patent. No new matter is added by this amendment of claim 5.

10. Support for amended claim 1 that we seek to present in this reissue application can be found in column 17, line 8 through column 21, line 12 (Examples 2-14), column 22, line 31 through column 23, line 33 (Examples 20-26), column 24, line 44 through column 25, line 38 (Examples 29-34), column 27, line 1 through column 23, line 29 (Examples 36-38) and column 29, line 1 through column 23, line 23 (Examples 41-61) of the '634 patent. Similarly,

support for amended claim 5 can be found in column 20, line 34 through column 21, line 12 (Examples 11-14) and column 27-28, line(s) 1 through column 27-28, line(s) 43 (Examples 36-38) thereof. Thus, claims 1 and 5 as proposed to be amended by this reissue recite alkylenediamine derivatives or salts thereof clearly and adequately described in the '634 patent.

11. It was also realized during said prosecution before the EPO, that, in order to obtain broader patent protection, a reissue application needed to be filed no later than September 29, 2000.

12. We acknowledge the duty to disclose information which is material to the examination of this application in accordance with 37 C.F.R. 1.56(a) and which occurred between the filing date of said prior application and the filing date of the application which issued as the '634 patent.

13. We hereby claim foreign priority benefits under Section 119 of Title 35, United States Code, of any foreign patent application for patent or inventor's certificate listed below and have also identified any foreign application for patent or inventor's certificate having a filing date before that of the application of which priority is claimed:

- (a) Japanese Patent Application No. 8-122195 filed on Apr. 18, 1996;
- (b) Japanese Patent Application No. 8-278871 filed on Sep. 30, 1996; and
- (c) Japanese Patent Application No. 9-12056 filed on Jan. 6, 1997.

Such priority benefits were claimed in USP 5,814,634, now sought to be reissued. Moreover, the disclosures of the above-identified priority documents were and continue to be incorporated herein by reference.

14. We hereby appoint Ronald R. Snider, Reg. No. 24,962, Elizabeth J. Pawlak, Reg. No. 34,520, Peter N. Lalos, Reg. No., 19,789, Francis A. Keegan, Reg. No. 19,245 to prosecute this application and to transact all business in the U.S. Patent and Trademark Office connected therewith. Please direct all telephone calls to: Ronald R. Snider, Esq., at telephone number (202) 347-2600, and all correspondence to:

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15. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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